Tetrahedron 67 (2011) 8685–8698

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A simple synthesis of the pentacyclic lamellarin skeleton from 3-nitro-2-(trifluoromethyl)-2*H*-chromenes and 1-methyl(benzyl)-3,4-dihydroisoquinolines

Vladislav Yu. Korotaev [a], Vyacheslav Ya. Sosnovskikh [a,*], Alexey Yu. Barkov [a], Pavel A. Slepukhin [b], Marina A. Ezhikova [b], Mikhail I. Kodess [b], Yurii V. Shklyaev [c]

[a] *Department of Chemistry, Ural State University, 620083 Ekaterinburg, Russia*
[b] *Institute of Organic Synthesis, Ural Branch of the Russian Academy of Sciences, 620990 Ekaterinburg, Russia*
[c] *Institute of Technical Chemistry, Ural Branch of the Russian Academy of Sciences, 614600 Perm, Russia*

ARTICLE INFO

Article history:
Received 25 May 2011
Received in revised form 25 August 2011
Accepted 12 September 2011
Available online 16 September 2011

Keywords:
Lamellarin skeleton
Grob reaction
3-Nitro-2-(trifluoromethyl)-2*H*-chromenes
3,4-Dihydroisoquinolines

ABSTRACT

The basic structural framework of lamellarin alkaloids, 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinoline derivatives, has been obtained in good yields via Grob synthesis between 3-nitro-2-(trifluoromethyl)-2*H*-chromenes and 1-methyl-3,4-dihydroisoquinolines in refluxing isobutanol. In the case of 1-benzyl-3,4-dihydroisoquinolines, a dynamic NMR effect was observed in the ^{1}H and ^{19}F NMR spectra of the products as a result of restricted rotation about the single bond linking the benzene ring and the heterocyclic system. When the reaction was carried out with 3-nitro-2-(trichloromethyl)-2*H*-chromenes in toluene at room temperature, only Michael adducts, as a mixture of two diastereomers, were isolated.

1. Introduction

Recently, considerable interest has been devoted to the synthesis of partially fluorinated heterocycles, many of which have found use as agrochemicals and drugs.[1] However, reports on the use of 2-(trifluoromethyl)-2*H*-chromenes as substrates for organic synthesis are very scarce, although 2*H*-chromene (2*H*-1-benzopyran) and its derivatives belong to an important class of oxygen-containing heterocyclic compounds that are common in plants and exhibit a wide spectrum of useful properties. Structures containing a benzopyran framework have antitumour, antibacterial and antiinflammatory activity and inhibit HIV-1 reverse transcriptase, interleukin-1 production and protein kinases and can cleave DNA.[2] In addition, they are also useful intermediates in the synthesis of complex natural products, such as pterocarpans.[3] In continuation of our studies on the chemical properties of 3-nitro-2-(trihalomethyl)-2*H*-chromenes (**1**, X=F, Cl),[4] which turned out to be highly reactive substrates in reactions with N-, S-, and C-nucleophiles,[5] we decided to investigate their reaction with 1-methyl(benzyl)-3,4-dihydroisoquinolines **2**. The latter are another group of biologically interesting compounds, which exhibit diverse biological properties including anticonvulsant, antimicrobiological and antitumour activities[6] and are capable of reacting with electrophilic substrates as C-nucleophiles or 1,3-C,N-dinucleophiles via the enamine tautomeric form.[7] Although much attention has been paid to the chemistry of 3,4-dihydroisoquinolines **2**, mainly due to their use as excellent building blocks for the preparation of a variety of complex heterocyclic compounds,[7] their reactions with 3-nitro-2*H*-chromenes have not been described in the literature. There is only one report on the reaction of ethyl (6,7-dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidene)acetate with 2-nitro-1-phenylpropene and 1-nitro-1,2-diphenylethene leading to the corresponding 5,6-dihydropyrrolo[2,1-*a*]isoquinoline derivatives.[8]

A reaction involving the addition of secondary enaminoesters to nitroolefins followed by intramolecular displacement of the nitro group by the amino group to yield pyrroles was disclosed by Grob et al.[9] This method makes use of easily prepared reagents and is particularly suitable for a combinatorial approach to the synthesis of substituted pyrroles.[10] Since imines, which exist in equilibrium with their enamines, have been shown to react with β-nitrostyrene to give the corresponding pyrroles,[11] it was expected that Michael addition of enamines derived from 1-methyl- and 1-benzyl-3,4-dihydroisoquinolines **2** to a powerful Michael acceptor, such as chromenes **1**, followed by ring closure and aromatization (Grob synthesis) could provide a direct route to 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolines **3** (Fig. 1).

This heterocyclic system constitutes the basic structural framework of the well-known lamellarin alkaloids **4** (for example,

* Corresponding author. E-mail addresses: sosn1951@mail.ru, vyacheslav.sosnovskikh@usu.ru (V.Y. Sosnovskikh).

0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.049

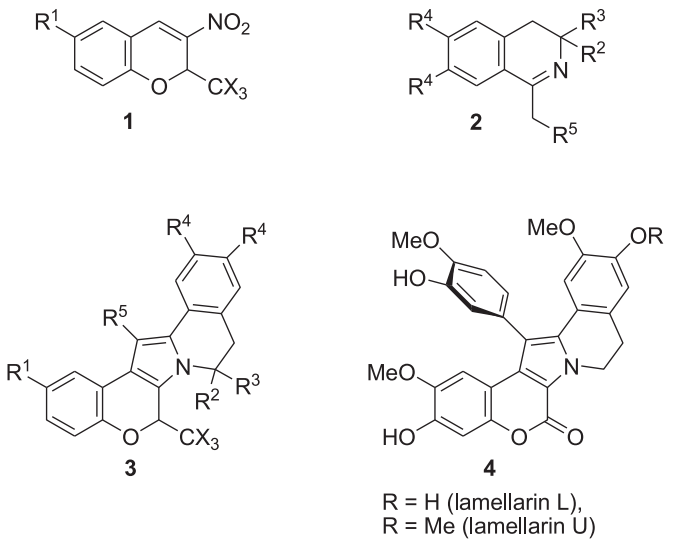


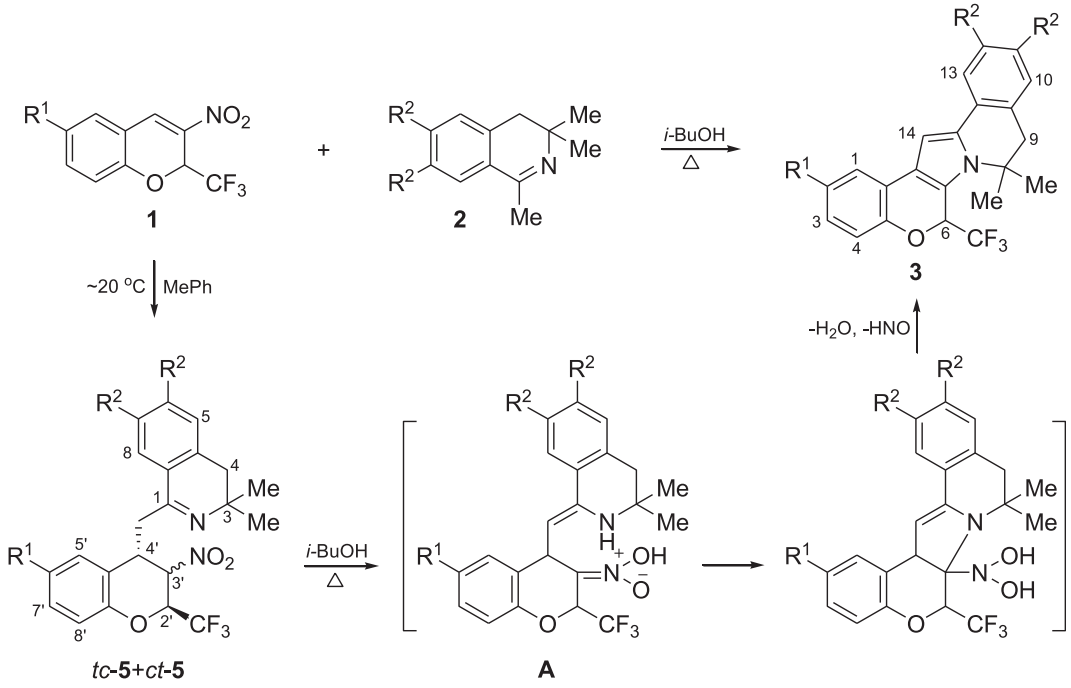
Fig. 1. Starting materials and target products.

lamellarins L and U), a family of marine natural products, which exhibit a wide range of biological activities.[12] The lamellarins and related naturally occurring pyrrole-derived alkaloids have shown promising cytotoxicity and antitumour activity, reversal of multidrug resistance (MDR), HIV-1 integrase inhibition, immunomodulation and antibiotic activity.[13] In addition, the lamellarins represent a new series of topoisomerase I inhibitors.[14] Therefore, the development of efficient new methods leading to this heterocyclic framework is highly desirable.[15]

Recently, it was reported that the reaction of 3-nitrocoumarins with 1-benzyl-3,4-dihydroisoquinolines gave the desired lamellarins in only 5–6% yields.[16] In this context, we anticipated that, if the reaction occurred with chromenes **1**, the pentacyclic lamellarin ring system would be constructed successfully in one chemical operation and a series of novel lamellarin derivatives would be accessible. Indeed, we have shown quite recently[17] that the reaction of 3-nitro-2-(trifluoromethyl)-2*H*-chromenes **1** (X=F) with 1,3,3-trimethyl-3,4-dihydroisoquinolines **2** gave 6-(trifluoromethyl)-8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*] isoquinolines **3**, while the reaction of 3-nitro-2-(trichloromethyl)-2*H*-chromenes **1** (X=Cl) stopped at the initial Michael addition stage. Herein, we report full details of this study. In addition to our preliminary communication,[17] some novel 8,9-dihydro-6*H*-chromeno[4′,3′:4,5]pyrrolo[2,1-*a*]isoquinolines as well as 2,3,4-trisubstituted chroman derivatives have been prepared and studied by X-ray diffraction analysis. In the case of 1-benzyl-3,4-dihydroisoquinolines, dynamic NMR effects are observed in the ^{1}H and ^{19}F NMR spectra.

2. Results and discussion

We found that 3-nitro-2-(trifluoromethyl)-2*H*-chromenes **1**, as the nitroolefin components, reacted with 1,3,3-trimethyl-3,4-dihydroisoquinolines **2**, as the enamine components, in toluene at room temperature for 1 h to give Michael adducts **5a**–**f** as a mixture of trans–cis (*tc*) and cis–trans (*ct*) isomers (ca. 1:1) in good to high combined yields (Scheme 1 and Table 1; in *tc*-**5** the '*t*' refers to the relative configurations at C-2′ and C-3′, and the '*c*' to the relationship between C-3′ and C-4′). The double bond of **1** is so reactive that no catalyst was necessary. Notably, the chroman products **5** contain three contiguous stereogenic centres, but in all cases, only two diastereomers could be observed by ^{1}H NMR spectroscopy of the crude reaction mixtures. The structures of **5** were characterized by ^{1}H, ^{19}F, ^{13}C NMR and elemental analyses.



Scheme 1. Synthesis of compounds **3** and **5**.

The most diagnostic parameter for structural assignment was the coupling constants between protons H-2′ and H-3′ and H-3′ and H-4′. In the cis–trans-isomer (*ct*-isomer) **5** the coupling constants $J_{2',3'}=J_{3',4'}=1.5$ Hz are significantly smaller and typical of a *gauche* conformation. The cis–trans configuration has been verified by comparison of spectral data obtained for *ct*-**5** with those appeared in literature. Earlier, $J_{2,3}=J_{3,4}=1.2$–1.8 Hz values were reported for cis–trans adducts formed in reactions of thiols and indoles with

Table 1
Synthesis of compounds **3a**–**f** and **5a**–**f**

R^1	R^2	Adduct **5**	Yield (%)	Product **3**	Yield[a] (%) Method A	Yield[b] (%) Method B
H	H	**5a**	68	**3a**	58	48
H	Me	**5b**	73	**3b**	67	60
H	MeO	**5c**	81	**3c**	56	25
MeO	MeO	**5d**	84	**3d**	77	42
Br	Me	**5e**	39	**3e**	63	26
Br	MeO	**5f**	86	**3f**	75	61

[a] From **5**.
[b] From **1** and **2**.

chromenes **1**[5a–c] and $J_{2,3}=J_{3,4}=2.2$ Hz for *cis*–*trans*-2-(4-chlorophenyl)-4-(indol-3-yl)-3-nitrochroman, whose structure was confirmed by X-ray diffraction analysis.[18] Additional evidence for the cis–trans configuration was obtained from the chemical shift in the narrow range δ 86.5–86.6 ppm (C_6F_6) and the coupling constant of the doublet for the CF_3 group ($^3J_{F,H}=5.7$–5.9 Hz), which agrees well with the literature data for cis–trans adducts of chromenes **1** with thiols[5a,b] and azoles.[5c] The trans–cis configuration (*tc*-isomer) was also evident from the experimental coupling constants $J_{2',3'}\approx J_{3',4'}\approx 4.5$ Hz, which correlate with the literature data for trans–cis adducts of thiols with chromenes **1**.[5a,b] A characteristic difference between the two stereoisomers is based on the chemical shift of the H-2′ proton, which was shifted downfield by 0.7–0.8 ppm in *tc*-isomer compared to *ct*-isomer. This is due to the deshielding effect of the NO_2 group, which is cis to H-2′ in the *tc*-isomer. Note that in some cases, the ^{1}H NMR spectra of the Michael adducts recorded at 298 K displayed broad signals for the aliphatic and aromatic protons. This phenomenon may be attributed to the restricted rotation of the dihydroisoquinoline moiety about the C–C single bond leading to rotamer formation.

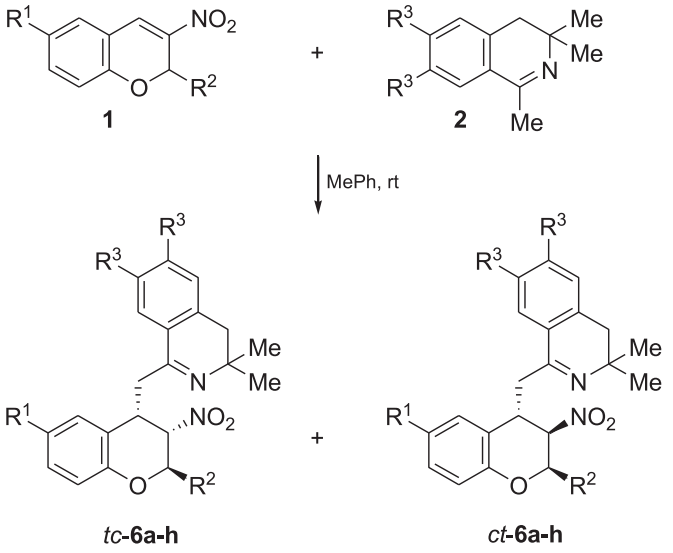
When chromans **5a**–**f** as a mixture of *tc*- and *ct*-diastereomers were heated at reflux in isobutanol for 1 h, pentacycles **3a**–**f** were obtained in good yields (method A). The progress of the reaction was monitored by TLC, and the results are summarized in Table 1. Among different solvents (alcohols, acetonitrile), isobutanol appeared to give the best results. It was also found that **1** and **2** could be employed directly under these conditions to give **3a**–**f** in 25–61% yields (method B), however, better yields and easier purification of compounds **3** were achieved if the transformation was performed in a two-step approach (method A). Thus, compounds **3** and **5** could be synthesized from the same starting material simply by the choice of the reaction conditions (Scheme 1). In accordance with the proposed mechanism,[9b] the Michael adduct **5** undergoes intramolecular displacement of the nitro group by the NH group, thus affording lamellarin system **3** via elimination of water and hyponitrous acid.

To the best of our knowledge, pentacycles **3** represent the first lamellarin derivatives reported to date bearing a CF_3 substituent instead of a carbonyl group. The structures of **3a**–**f** were confirmed with the help of spectral and analytical data. For example, the ^{1}H NMR spectrum of compounds **3b** in $CDCl_3$ showed two AX doublets ($J_{AX}=15.4$ Hz) at δ 2.70 and 3.13 ppm for the CH_2 group and a quartet at δ 6.14 ppm ($^3J_{H,F}=6.1$ Hz) due to the H-6 proton. The pyrrole ring proton resonated at δ 6.77 ppm. In the ^{19}F NMR spectrum the CF_3 group of **3b** appeared as a doublet with $^3J_{F,H}=6.1$ Hz at 86.43 ppm (C_6F_6). The ^{13}C NMR spectrum of **3b** exhibited a quartet ($^1J_{C,F}=288.0$ Hz) at 123.6 ppm for the carbon of the CF_3 group and a quartet ($^2J_{C,F}=32.6$ Hz) at 71.2 ppm for the *C*–CF_3 atom. This confirmed that the CF_3 group is bonded to the sp^3 hybridized carbon atom. In addition, another feature of interest was the appearance of a quartet ($^6J_{C,F}=2.4$ Hz) at 26.4 ppm due to one of the C(8)–Me groups, indicating that the Me and CF_3 groups were spatially close to each other.

We next investigated the reaction of 3-nitro-2-(trichloromethyl)-2*H*-chromenes **1** ($R^2=CCl_3$), with 1,3,3-trimethyl-3,4-dihydroisoquinolines **2** in order to prepare CCl_3-containing pentacycles of type **3**. When 2-CCl_3-chromenes **1** were reacted in toluene at room temperature for 1 h, the reaction proceeded smoothly to give, both prior to and after recrystallization, an unequal mixture of *trans*–*cis* and *cis*–*trans* chromans **6a**–**f** substantially favouring the trans–cis-isomer (85:15 in $CDCl_3$). This result shows that the isomer ratio depends on the steric effects of the trihalomethyl group (Scheme 2, Table 2).

Table 2
Synthesis of compounds **6a**–**h**

Adduct **6**	R^1	R^2	R^3	Yield (%)
6a	H	CCl_3	H	60
6b	H	CCl_3	Me	78
6c	H	CCl_3	MeO	71
6d	MeO	CCl_3	MeO	62
6e	Br	CCl_3	Me	52
6f	Br	CCl_3	MeO	58
6g	H	Ph	H	64
6h	H	Ph	MeO	91



Scheme 2. Synthesis of compounds **6**.

The structures of compounds **6** compare well with the results of elemental analysis, ^{1}H, ^{13}C NMR and IR spectroscopy. The diastereomeric ratio was determined by ^{1}H NMR spectroscopic analysis. In this case, the coupling constants for the trans–cis-isomers are $J_{2',3'}\approx J_{3',4'}\approx 5.0$ Hz and those for the cis–trans-isomers are $J_{2',3'}=J_{3',4'}=1.5$ Hz. The stereochemistry of the *tc*-isomer **6b** and *ct*-isomer **6g** were independently confirmed by X-ray crystal structure analysis (Figs. 2 and 3). It should be noted that on dissolution in DMSO-d_6, the ratio of the isomers changed to *tc*-**6**/*ct*-**6**=35:65 (for compounds **5** in DMSO-d_6 it was *tc*-**5**/*ct*-**5**=15:85). Isomerization to this extent is evident immediately on dissolution (after 1–2 min), and at constant temperature there was no subsequent change in the percentage isomerization. This is associated with epimerization at the C-3 atom and indicates the higher thermodynamic stability of the cis–trans-isomer of 2-CX_3-chromans **5** and **6**, especially for **5** (X=F). Of the four possible diastereomers (trans–trans, cis–cis, trans–cis, and cis–trans), the dehydroisoquinoline fragment and trihalomethyl substituent are trans to each other only in the last two isomers, which probably control the stereochemistry of the Michael addition (Scheme 3).

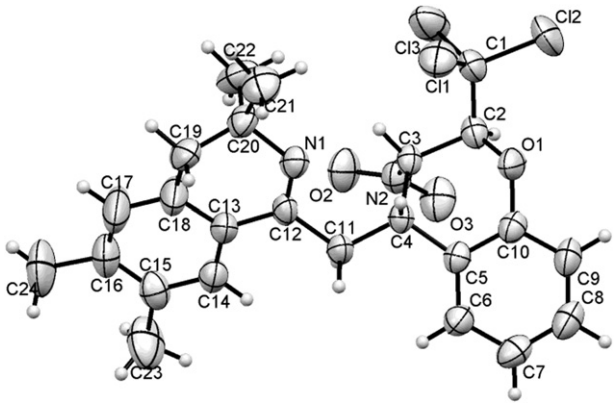


Fig. 2. Molecular structure of *tc*-**6b** (thermal ellipsoids at 50% probability).

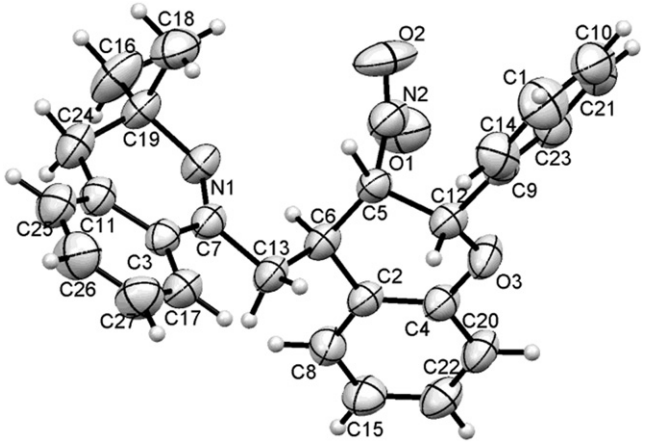


Fig. 3. Molecular structure of *ct*-**6g** (thermal ellipsoids at 50% probability).

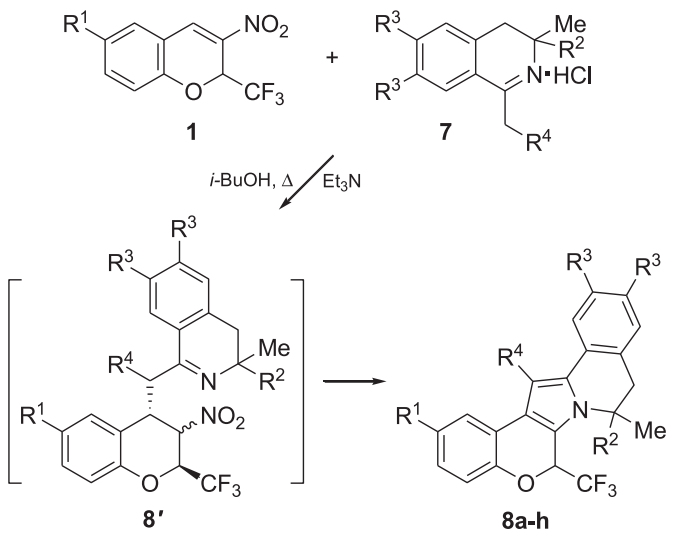
tc-**5,6** ($J_{2,3}$ ~ $J_{3,4}$ = 4.5-5.0 Hz) *ct*-**5,6** ($J_{2,3}$ ~ $J_{3,4}$ = 1.5 Hz)

tc-**5**:*ct*-**5** = 55:45 ($CDCl_3$), *tc*-**5**:*ct*-**5** = 15:85 (DMSO-d_6);
tc-**6**:*ct*-**6** = 85:15 ($CDCl_3$), *tc*-**6**:*ct*-**6** = 35:65 (DMSO-d_6)

Scheme 3. Epimerization at the C-3 atom of compounds **5** and **6**.

Unfortunately, attempts to cyclise trichloromethylated Michael adducts **6** in the usual manner (methods A and B) gave only multicomponent reaction mixtures from which no fused pyrroles of type **3** could be isolated. Thus, the reaction turned out to be very sensitive to the nature of the CX_3 substituent and afforded pyrroles **3** only when the 2-CF_3-chromenes **1** were used. This is probably a result of the equilibrium between the nitro and *aci* forms of the Michael adduct. It seems that the CF_3 group, due to its powerful electron-withdrawing character, favours a preponderance of the latter form **A** (Scheme 1), from which the pyrroles **3** are derived. Another reason may be a weak C(4′)–CH_2 linkage in **6**, since partial decomposition in DMSO-d_6 took place and starting materials **1** and **2** were observed in the ^{1}H NMR spectra. It should be noted that the reaction of 3-nitro-2-phenyl-2*H*-chromene[19] **1** (R^1=H, R^2=Ph) with **2** (R^3=H, MeO) also stops at the Michael addition stage to give chromans **6g**,**h** as a mixture of cis–trans and trans–cis diastereomers (~9:1 in DMSO-d_6) and all our attempts to synthesize from these compounds the corresponding lamellarin derivatives failed.

It was also found that the hydrochlorides of 1-methyl- and 1-benzyl-3,4-dihydroisoquinolines **7** bearing one or two methyl groups at the 3-position reacted with 2-CF_3-chromenes **1** at reflux in isobutanol for 3 h in the presence of triethylamine (1.2 equiv) to give pentacycles **8a**–**h** as the only isolated products in variable yields 23–78% (Scheme 4, Table 3). This result clearly shows that the present reaction could be applicable to various types of 3,4-dihydroisoquinolines, providing a simple and rapid route to the synthesis of a great variety of CF_3-containing benzopyrano[3,4-*b*]pyrroles with potential biological activity. In the case of 1-benzyl-3,4-dihydroisoquinolines **7**, we were also intrigued by the fact that benzopyrano[3,4-*b*]pyrroles were structurally reminiscent of axially chiral biaryl compounds and might display restricted rotation about the C(14)–C(1′) single bond and, depending on the energetic barrier to rotation, be resolved into two diastereomeric atropisomeric forms.



Scheme 4. Synthesis of compounds **8**.

Table 3
Synthesis of compounds **8a**–**h**

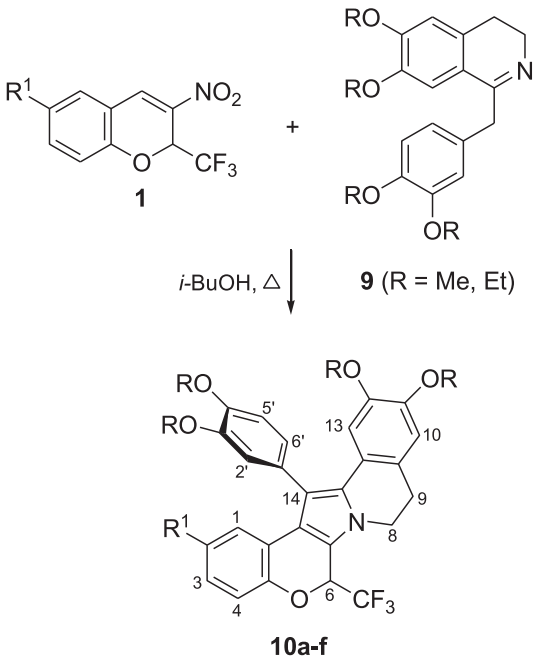
Product **8**	R^1	R^2	R^3	R^4	Yield (%)
8a	H	H	MeO	H	78
8b	MeO	H	MeO	H	44
8c	Br	H	MeO	H	48
8d	Br	H	MeO	3,4-$(MeO)_2C_6H_3$	51
8e	H	Me	H	Ph	39
8f	H	Me	Me	Ph	39
8g	Br	Me	Me	Ph	38
8h	Br	Me	BuO	Ph	23

Compounds **8a**–**c** (R^2=R^4=H) were obtained as a mixture of trans- (53–86%) and cis-isomers (14–47%), the relative stereochemistry of which was determined by ^{13}C NMR spectroscopy. Although, we were unable to isolate them in pure form, the NMR data for each isomer can be extracted from the spectrum of the mixture (see Experimental section). The ^{13}C NMR spectra of **8a**,**c** in $CDCl_3$ revealed a quartet at 19.5 ppm with $^6J_{C,F}$=2.6–2.9 Hz and a singlet at 20.3–20.4 ppm due to the C(8)–Me group of the cis- and trans-isomers, respectively. Assignment of all signals in the ^{1}H and ^{13}C NMR spectra of **8c** was performed based on results of 2D ^{1}H–^{13}C HSQC and HMBC experiments. In the case of compounds **8e**–**h** (R^2=Me, R^4=Ph), the steric interactions between the benzene ring

and the *peri*-hydrogens disfavour co-planarity of the system, which adopts a twisted conformation. In fact, **8e**–**h** possess a conformational stereogenic axis and, in addition, a configurational stereogenic centre. Due to restricted rotation of the phenyl ring at C-14, these compounds exist in solution as a mixture of two diastereomeric rotamers (see below), while benzopyrano[3,4-*b*]pyrrole **8d** (one chiral axis and two chiral centres) exists as a mixture of rotamers of trans- (87%) and cis-isomers (13%). It should be noted that in the case of 3,4-dihydroisoquinolines **7**, the intermediates **8′** could not be isolated and underwent spontaneous cyclization to form the fused pyrrole ring (Scheme 4). Attempts to synthesize compounds **8′** in toluene at room temperature failed.

As an extension of this cyclization for the synthesis of biologically interesting non-natural lamellarin analogues we studied the reaction of 2-CF_3-chromenes **1** with 1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline (dihydropapaverine **9**, R=Me) and 1-(3,4-diethoxy-benzyl)-6,7-diethoxy-3,4-dihydroisoquinoline (drotaverine **9**, R=Et).[20] The hydrochloride of the latter is a well-known spasmolytic agent widely used in medicine and known as No-Spa. We anticipated that these new analogues prepared from **1** and **9** and differing from lamellarins **4** only by replacement of the oxo group with CF_3 one can serve as a basis for the search of new physiologically active compounds.

We found that dihydropapaverine and drotaverine bases or hydrochlorides reacted with 2-CF_3-chromenes **1** in a desired manner under reflux in isobutanol for 45 min to produce compounds **10a**–**f** in 64–92% yields (Scheme 5, Table 4). Since 1-benzyl-3,4-dihydroisoquinolines **9** are prone to air oxidation to give 3,4-dihydropapaveraldine and drotaveraldine,[21] all operations should be preformed in an inert atmosphere. Reactions of 3-nitro-2-(trichloromethyl)- and 3-nitro-2-phenyl-2*H*-chromenes with dihydroisoquinolines **7** and **9** did not give the corresponding lamellarin derivatives even under more drastic conditions.



Scheme 5. Synthesis of compounds **10**.

In the course of our studies of **10a**–**f** and related substances **8d**–**h** we have consistently noticed exchange broadening of ^1H, ^{19}F and ^{13}C NMR signals for spectra ran in $CDCl_3$ and DMSO-d_6 solutions at room temperature, which can be overcome by heating to

Table 4
Synthesis of compounds **10a**–**f**

Product **10**	R	R^1	Yield (%)
10a	Me	H	78
10b	Me	MeO	66
10c	Me	Br	92
10d	Et	H	81
10e	Et	MeO	71
10f	Et	Br	64

100–120 °C (DMSO-d_6). All signals in the ^1H and ^{13}C NMR spectra of compound **10a** were assigned on the basis of 2D ^1H–^1H COSY, ^1H–^{13}C HSQC and HMBC experiments at 100 °C. The structures of compounds **10b**–**f** were firmly established by comparison of their spectra with the spectra of **10a**. A characteristic feature of the ^1H NMR spectra is the presence of quartet at δ 5.69–5.75 ppm with $^3J_{H,F}$=6.0–6.4 Hz in $CDCl_3$ for H-6 proton (δ 6.49–6.64 ppm, $^3J_{H,F}$=6.8–6.9 Hz in DMSO-d_6). It is well-known that the aromatic group on the pyrrole ring is almost orthogonal to the rest of the relatively planar pentacyclic system of lamellarins **1** to avoid severe steric interactions.[12] Keeping this fact in mind and in making the ^1H NMR assignments, we have assumed that the ring current of the phenyl ring attached at C-14 causes shielding of the protons at C-1, C-13, C-12 and C-2.[12] In all cases, the ^1H NMR spectra of **8d**–**h** and **10a**–**f** recorded in $CDCl_3$ and DMSO-d_6 at room temperature displayed broadened signals in both the aromatic (mainly Ar–C(14)) and aliphatic region due to the restricted rotation of the aryl moiety about the C(14)–C(1′) bond leading to atropisomers (interconverting rotational isomers) (Fig. 4). This process was studied by variable temperature (VT) ^1H and ^{19}F NMR measurements for compound **10a** as a typical case, which showed distinct temperature-dependent behaviour.

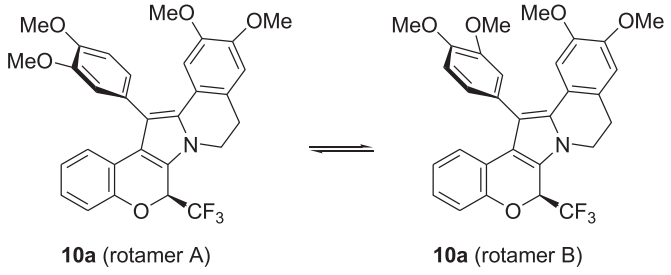


Fig. 4. Interconverting rotational isomers **10a**.

The observed spectra of **10a** are shown in Figs. 5 and 6. The ^1H NMR spectrum (500 MHz) recorded at 297 K in DMSO-d_6 solution showed pronounced line broadening of all the resonances suggesting slow intramolecular motions in the system. A single set of well resolved signals was observed above 373 K (Fig. 5). At low temperature (below 253 K, CD_2Cl_2), the protons of the benzene rings appear as a complex multiplet in the aromatic region, whereas the H-13, MeO and CF_3 signals split into two sets, indicating a 46:54 mixture of rotamers A and B, the ratio of which was measured by integration of the well resolved H-13 protons (δ 6.45 and 6.53 ppm) and CF_3 groups (δ 83.7 and 83.9 ppm) (Fig. 6). Note that the spectra of **10a** showed one singlet (6H) for two MeO–C11 and MeO–C3′ groups by chance.

Although complete line shape analysis was not undertaken in the present work, the variable temperature ^1H and ^{19}F NMR spectra from 183 to 293 K allowed calculating the rotation energy barrier for the dynamic NMR process in **10a**.[22] The signals attributed to the aromatic H-13 proton ($\Delta\nu$=43.0 Hz) and the CF_3 group ($\Delta\nu$=75.0 Hz) coalesced at 285 K, and the barrier to rotation was estimated to be $\Delta G^{\ddagger}$=13.0 kcal/mol. The $\Delta G^{\ddagger}$ value for **10a**, obtained from VT NMR

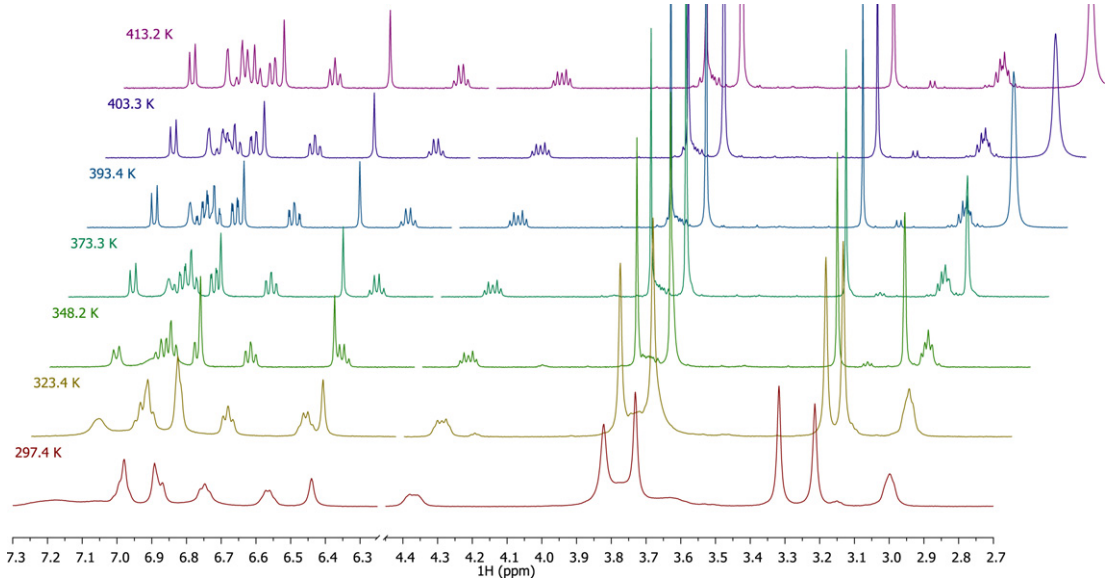


Fig. 5. VT ^{1}H NMR spectra of **10a** in DMSO-d_6 in the range 297–413 K (signals at δ 3.2–2.7 ppm due to H_2O in solvent).

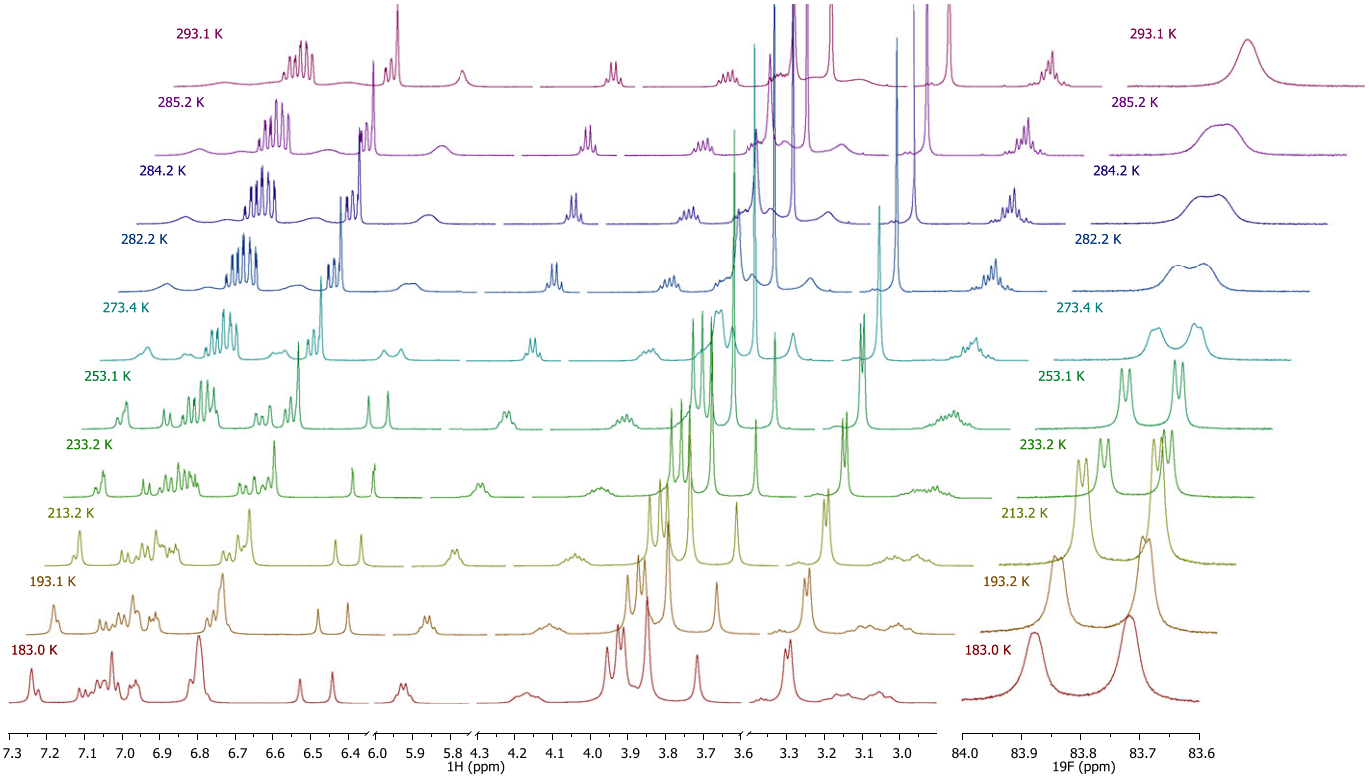


Fig. 6. VT ^{1}H and ^{19}F NMR spectra of **10a** in CD_2Cl_2 in the range 183–293 K.

measurements, shows that rotamers A and B can be interconverted by overcoming energy barrier of 13.0 kcal/mol. For the isolation of the rotamers at room temperature, it should be noted that a free energy of activation higher than ca. 23 kcal/mol is required.[23] Thus, compounds **10** belong to the class possessing a rather low energy barrier to rotation about the C(14)–C(1′) bond and could not be isolated as diastereomerically pure atropisomers.

We were also interested in examining the utility of this method with different benzofused chromenes **11a**,**b**, prepared from (*E*)-3,3,3-trifluoro-1-nitropropene and 2-hydroxy-1-naphthaldehyde and 1-hydroxy-2-naphthaldehyde.[4] As expected, the nucleophilic attack depends on the steric effects and no reaction occurred when **11a** was used. The failure of the cyclocondensation with **11a** results possibly from the bulky benzene ring, which hinders the approach to the nitroolefin fragment and unfavourable steric interactions become the deciding factor. On the other hand, unlike chromene **11a**, isomeric chromene **11b** was successfully employed for the reaction with dihydropapaverine **9** (R=Me). When **11b** and **9** were heated in isobutanol for 45 min, heterocyclization proceeded smoothly to give compound **12** in 94% yield, the structure of which was established by comparison of its ^{1}H NMR spectrum with the spectrum of compound **10a** (Fig. 7).

In conclusion, the current reaction represents a facile method for the preparation of a diverse range of new pentacyclic lamellarin

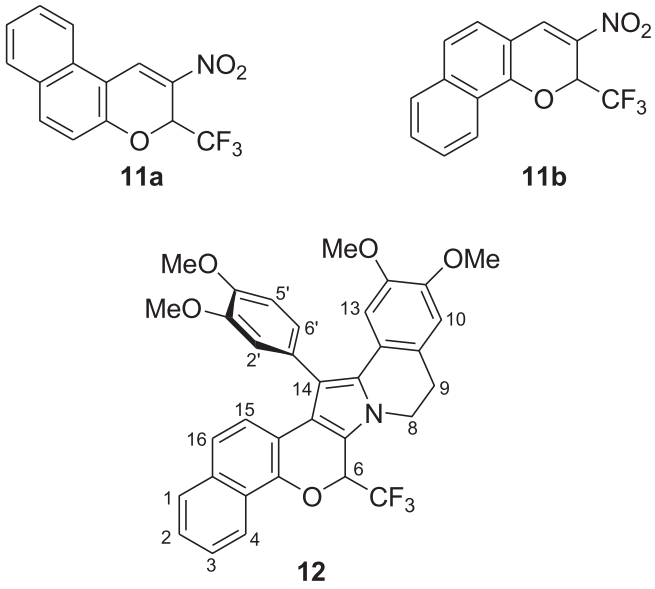


Fig. 7. Benzofused chromenes **11a** and **11b** and the product **12** from the latter.

derivatives via simple annulation of a pyrrole ring to chromenes, an important structural moiety found in many bioactive natural products. The substrate scope was broadly studied, and the incorporation of a trifluoromethyl group made these compounds potentially interesting substrates for drug discovery.

3. Experimental

3.1. General

NMR spectra were recorded on a Bruker DRX-400 (^{1}H—400 MHz, ^{13}C—100 MHz and ^{19}F—376 MHz) and AVANCE-500 (^{1}H—500 MHz, ^{13}C—126 MHz and ^{19}F—471 MHz) spectrometers in DMSO-d_6 and $CDCl_3$ with TMS and C_6F_6 as internal standards, respectively. IR spectra were recorded on a Perkin–Elmer Spectrum BX-II instrument as KBr discs. Mass spectra were obtained with the TurboMass (Perkin–Elmer) mass spectrometer. Elemental analyses were performed at the Microanalysis Services of the Institute of Organic Synthesis, Ural Branch, Russian Academy of Sciences. All solvents used were dried and distilled per standard procedures. The starting 3-nitro-2*H*-chromenes **1** were prepared according to described procedures.[4,19]

3.2. General procedures for the synthesis of compounds 3

Method A. A mixture of the corresponding *tc*- and *ct*-chromanes **5** (1.0 mmol) was refluxed in isobutanol (2 mL) for 1 h. After that, the mixture was concentrated under reduced pressure and the solid formed was recrystallized from dichloromethane/hexane (1:2) to give compound **3** as a colourless powder.

Method B. A mixture of the corresponding chromene **1** (1.0 mmol) and dihydroisoquinoline **2** (1.0 mmol) was refluxed in isobutanol (2 mL) for 1 h. After that, the mixture was concentrated under reduced pressure and the solid formed was recrystallized from dichloromethane/hexane (1:2) to give compound **3**.

*3.2.1. 8,8-Dimethyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno [4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**3a**).* Yield 0.21 g (58%, *A*), 0.18 g (48%, *B*), mp 141–142 °C; IR (KBr) 1635, 1616, 1592, 1560, 1532, 1498 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (s, 3H, Me), 1.80 (s, 3H, Me), 2.78 (d, 1H, H-9′, J=15.4 Hz), 3.20 (d, 1H, H-9″, J=15.4 Hz), 6.15 (q, 1H, H-6, J=6.0 Hz), 6.83 (s, 1H, H-14), 6.99–7.31 (m, 6H, arom.), 7.46 (dd, 1H, H-1/13, J=7.4, 1.1 Hz), 7.60 (d, 1H, H-13/1, J=7.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.5 (d, CF_3, J=6.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.5 (q, Me′-8, $^6J_{C,F}$=2.3 Hz), 27.9 (Me″-8), 45.3 (C-9), 58.3 (C-8), 71.2 (q, C-6, $^2J_{C,F}$=32.6 Hz), 99.3 (C-14), 115.7, 116.3, 119.1, 120.6, 122.3, 122.6, 122.7, 123.6 (q, CF_3, $^1J_{C,F}$=289.0 Hz), 126.7, 126.9, 127.3, 128.0, 128.5, 130.0, 134.3, 149.4. Anal. Calcd for $C_{22}H_{18}F_3NO$: C, 71.54; H, 4.91; N, 3.79. Found: C, 71.51; H, 4.87; N, 3.73.

*3.2.2. 8,8,11,12-Tetramethyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**3b**).* Yield 0.27 g (67%, *A*), 0.24 (60%, *B*), mp 178–179 °C; IR (KBr) 1635, 1616, 1592, 1560, 1532, 1498 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34, 1.78, 2.27, 2.30 (all s, 3H, Me), 2.70 (d, 1H, H-9′, J=15.4 Hz), 3.13 (d, 1H, H-9″, J=15.4 Hz), 6.14 (q, 1H, H-6, J=6.1 Hz), 6.77 (s, 1H, H-14), 6.93 (s, 1H, H-10), 7.00 (dd, 1H, H-4, J=7.5, 1.3 Hz), 7.02 (td, 1H, H-2, J=7.5, 1.3 Hz), 7.10 (td, 1H, H-3, J=7.5, 1.7 Hz), 7.38 (s, 1H, H-13), 7.45 (dd, 1H, H-1, J=7.5, 1.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.4 (d, CF_3, J=6.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (2C), 26.4 (q, Me′-8, $^6J_{C,F}$=2.4 Hz), 28.0 (Me″-8), 44.9 (C-9), 58.3 (C-8), 71.2 (q, C-6, $^2J_{C,F}$=32.6 Hz), 98.6 (C-14), 115.7, 115.9, 118.9, 120.8, 122.3, 122.5, 123.6 (q, CF_3, $^1J_{C,F}$=288.0 Hz), 123.9, 126.1, 126.8, 127.5, 129.2, 134.5, 135.3, 135.4, 149.4; MS (EI, 70 eV) *m*/*z* 397 $[M]^+$ (16), 328 $[M-CF_3]^+$ (100), 285 (24), 157 (20), 149 (12), 142 (11). Anal. Calcd for $C_{24}H_{22}F_3NO$: C, 72.53; H, 5.58; N, 3.52. Found: C, 72.62; H, 5.67; N, 3.50.

*3.2.3. 11,12-Dimethoxy-8,8-dimethyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**3c**).* Yield 0.24 g (56%, *A*), 0.11 g (25%, *B*), mp 171–172 °C; IR (KBr) 1638, 1615, 1563, 1536, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H, Me), 1.79 (s, 3H, Me), 2.69 (d, 1H, H-9′, J=15.2 Hz), 3.14 (d, 1H, H-9″, J=15.2 Hz), 3.91 (s, 3H, MeO), 3.96 (s, 3H, MeO), 6.14 (q, 1H, H-6, J=6.1 Hz), 6.68 (s, 1H, H-10), 6.71 (s, 1H, H-14), 7.00 (dd, 1H, H-4, J=7.4, 1.2 Hz), 7.02 (td, 1H, H-2, J=7.4, 1.2 Hz), 7.10 (s, 1H, H-13), 7.10 (td, 1H, H-3, J=7.4, 1.5 Hz), 7.45 (dd, 1H, H-1, J=7.4, 1.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.4 (d, CF_3, J=6.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 26.3 (q, Me′-8, $^6J_{C,F}$=2.4 Hz), 27.9 (Me″-8), 44.9 (C-9), 56.0 (Me-11), 56.1 (Me-12), 58.4 (C-8), 71.2 (q, C-6, $^2J_{C,F}$=32.5 Hz), 98.1 (C-14), 106.3 (C-13), 111.2 (C-10), 115.7 (C-4), 115.8 (C-6a), 119.0 (C-14a), 120.7 (C-14b), 121.3 (C-13a), 122.3 (C-1), 122.5 (C-2), 122.7 (C-9a), 123.6 (q, CF_3, $^1J_{C,F}$=288.7 Hz), 126.8 (C-3), 134.4 (C-13b), 148.3 (C-11), 148.4 (C-12), 149.4 (C-4a). Anal. Calcd for $C_{24}H_{22}F_3NO_3$: C, 67.13; H, 5.16; N, 3.26. Found: C, 67.05; H, 5.15; N, 3.22.

*3.2.4. 2,11,12-Trimethoxy-8,8-dimethyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**3d**).* Yield 0.34 (77%, *A*), 0.19 (42%, *B*), mp 177–178 °C; IR (KBr) 1627, 1610, 1565, 1534, 1507, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.35 (s, 3H, Me), 1.79 (s, 3H, Me), 2.69 (d, 1H, H-9′, J=15.3 Hz), 3.15 (d, 1H, H-9″, J=15.3 Hz), 3.83, 3.91, 3.97 (all s, 3H, MeO), 6.09 (q, 1H, H-6, J=6.1 Hz), 6.64 (dd, 1H, H-3, J=8.7, 2.9 Hz), 6.68 (s, 2H, H-10, H-14), 6.92 (d, 1H, H-4, J=8.7 Hz), 6.99 (d, 1H, H-1, J=2.9 Hz), 7.10 (s, 1H, H-13); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.7 (d, CF_3, J=6.1 Hz). Anal. Calcd for $C_{25}H_{24}F_3NO_4$: C, 65.35; H, 5.27; N, 3.05. Found: C, 65.19; H, 5.26; N, 2.96.

*3.2.5. 2-Bromo-8,8,11,12-tetramethyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**3e**).* Yield 0.30 g (63%, *A*), 0.12 g (26%, *B*), mp 197–198 °C; IR (KBr) 1608, 1558, 1530, 1498 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33 (s, 3H, Me), 1.78 (s, 3H, Me), 2.27 (s, 3H, Me), 2.30 (s, 3H, Me), 2.70 (d, 1H, H-9′, J=15.4 Hz), 3.13 (d, 1H, H-9″, J=15.4 Hz), 6.13 (q, 1H, H-6, J=6.0 Hz), 6.74 (s, 1H, H-14), 6.87 (d, 1H, H-4, J=8.5 Hz), 6.94 (s, 1H, H-10), 7.17 (dd, 1H, H-3, J=8.5, 2.4 Hz), 7.37 (s, 1H, H-13), 7.55 (d, 1H, H-1, J=2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.4 (d, CF_3, J=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6 (2C), 26.4 (q, Me′-8, $^6J_{C,F}$=2.4 Hz),

28.0 (Me″-8), 44.8 (C-9), 58.5 (C-8), 71.3 (q, C-6, $^{2}J_{C,F}$=32.6 Hz), 98.6 (C-14), 115.0, 116.1, 117.4, 117.9, 122.9, 123.4 (q, CF_3, $^{1}J_{C,F}$=288.8 Hz), 124.0, 125.0, 125.9, 127.5, 129.2 (2C), 134.8, 135.5, 135.6, 148.4; MS (EI, 70 eV) *m/z* 477 $[M+1]^+$ (12), 475 $[M-1]^+$ (12), 408 $[M+1-CF_3]^+$ (92), 406 $[M-1-CF_3]^+$ (92), 365 (18), 363 (18), 197 (18), 188 (18). Anal. Calcd for $C_{24}H_{21}BrF_3NO$: C, 60.52; H, 4.44; N, 2.94. Found: C, 60.45; H, 4.37; N, 3.00.

*3.2.6. 2-Bromo-11,12-dimethoxy-8,8-dimethyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**3f**).* Yield 0.38 g (75%, *A*), 0.31 g (61%, *B*), mp 195–196 °C; IR (KBr) 1633, 1614, 1557, 1532, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 3H, Me), 1.79 (s, 3H, Me), 2.69 (d, 1H, H-9′, *J*=15.4 Hz), 3.15 (d, 1H, H-9″, *J*=15.4 Hz), 3.91 (s, 3H, MeO), 3.96 (s, 3H, MeO), 6.14 (q, 1H, H-6, *J*=6.0 Hz), 6.68 (s, 2H, H-10, H-14), 6.88 (d, 1H, H-4, *J*=8.5 Hz), 7.08 (s, 1H, H-13), 7.18 (dd, 1H, H-3, *J*=8.5, 2.4 Hz), 7.56 (d, 1H, H-1, *J*=2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.4 (d, CF_3, *J*=6.0 Hz). Anal. Calcd for $C_{24}H_{21}BrF_3NO_3$: C, 56.71; H, 4.16; N, 2.76. Found: C, 56.60; H, 3.86; N, 2.87.

3.3. General procedures for the synthesis of compounds 5 and 6

A solution of the corresponding chromene **1** (1.0 mmol) and dihydroisoquinoline **2** (1.0 mmol) in toluene (2 mL) was kept at room temperature. After that, the mixture was concentrated under reduced pressure and the solid formed was washed with hexane and recrystallized from dichloromethane–hexane to give compound **5** or **6** as a colourless powder, except **6b** and **6g**, which were obtained as colourless crystals.

*3.3.1. 3,3-Dimethyl-1-[3-nitro-2-(trifluoromethyl)chroman-4-yl]methyl-3,4-dihydroisoquinoline (**5a**).* Yield 0.29 g (68%, 4 days), mp 111–112 °C; IR (KBr) 1617, 1583, 1562, 1490, 1372 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 54%) δ 1.15 (s, 3H, Me), 1.19 (s, 3H, Me), 2.67 (AB-system, 2H, H-4, *J*=16.3 Hz), 3.08 (dd, 1H, C*H*H, *J*=16.8, 8.5 Hz), 3.31 (dd, 1H, CH*H*, *J*=16.8, 6.0 Hz), 4.31 (ddd, 1H, H-4′, *J*=8.5, 6.0, 4.6 Hz), 5.29 (qd, 1H, H-2′, *J*=6.0, 4.6 Hz), 5.84 (t, 1H, H-3′, *J*=4.6 Hz), 7.00–7.45 (m, 8H, arom.), (*ct*, 46%) δ 1.21 (s, 3H, Me), 1.23 (s, 3H, Me), 2.74 (s, 2H, H-4), 2.79 (dd, 1H, C*H*H, *J*=16.7, 11.8 Hz), 3.39 (dd, 1H, CH*H*, *J*=16.7, 3.0 Hz), 4.05 (dd, 1H, H-4′, *J*=11.8, 3.0 Hz), 4.58 (q, 1H, H-2′, *J*=5.7 Hz), 5.57 (s, 1H, H-3′), 7.00–7.45 (m, 8H, arom.); ^{19}F NMR (376 MHz, $CDCl_3$) (*tc*, 52%) δ 85.1 (br d, CF_3, *J*=6.0 Hz), (*ct*, 48%) δ 86.5 (br d, CF_3, *J*=5.7 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 86%) δ 1.14 (s, 3H, Me), 1.15 (s, 3H, Me), 2.73 (s, 2H, H-4), 3.28 (dd, 1H, C*H*H, *J*=17.7, 4.2 Hz), 3.34 (dd, 1H, CH*H*, *J*=17.7, 10.5 Hz), 4.02 (dd, 1H, H-4′, *J*=10.5, 4.2 Hz), 5.52 (qd, 1H, H-2′, *J*=6.3, 1.5 Hz), 5.60 (d, 1H, H-3′, *J*=1.5 Hz), 7.03 (d, 1H, H-8′, *J*=8.1 Hz), 7.08 (t, 1H, H-6′, *J*=7.6 Hz), 7.23–7.27 (m, 2H, arom.), 7.33 (t, 1H, *J*=7.6 Hz, arom.), 7.40–7.48 (m, 2H, arom.), 7.57 (d, 1H, H-5′, *J*=7.6 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) (*ct*, 84%) δ 88.2 (d, CF_3, *J*=6.3 Hz), (*tc*, 16%) δ 87.8 (d, CF_3, *J*=7.2 Hz). Anal. Calcd for $C_{22}H_{21}F_3N_2O_3$: C, 63.15; H, 5.06; N, 6.70. Found: C, 62.87; H, 4.89; N, 6.50.

*3.3.2. 3,3,6,7-Tetramethyl-1-[3-nitro-2-(trifluoromethyl)chroman-4-yl]methyl-3,4-dihydroisoquinoline (**5b**).* Yield 0.33 g (73%, 3 h), mp 116–117 °C; IR (KBr) 1618, 1583, 1565, 1491, 1371 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 50%) δ 1.13, 1.17, 2.26, 2.27 (all s, 3H, Me), 2.59 (AB-system, 2H, H-4, *J*=16.4 Hz), 3.05 (dd, 1H, C*H*H, *J*=16.7, 8.4 Hz), 3.27 (dd, 1H, CH*H*, *J*=16.7, 5.6 Hz), 4.30 (dt, 1H, H-4′, *J*=8.4, 5.6 Hz), 5.23–5.32 (m, 1H, H-2′), 5.85 (t, 1H, H-3′, *J*=4.4 Hz), 6.92 (s, 1H, H-5), 7.00–7.13 (m, 2H, arom.), 7.17 (s, 1H, H-8), 7.21–7.30 (m, 2H, arom.), (*ct*, 50%) δ 1.18, 1.21, 2.27, 2.28 (all s, 3H, Me), 2.65 (br s, 2H, H-4), 2.78 (dd, 1H, C*H*H, *J*=16.7, 12.0 Hz), 3.35 (dd, 1H, CH*H*, *J*=16.7, 3.0 Hz), 4.05 (dd, 1H, H-4′, *J*=12.0, 3.0 Hz), 4.58 (q, 1H, H-2′, *J*=5.9 Hz), 5.56 (br s, 1H, H-3′), 6.96 (s, 1H, H-5), 7.00–7.13 (m, 2H, arom.), 7.17 (s, 1H, H-8), 7.21–7.30 (m, 2H, arom.); ^{19}F NMR (376 MHz, $CDCl_3$) (*tc*, 50%) δ 85.1 (d, CF_3, *J*=6.6 Hz), (*ct*, 50%) δ 86.5 (d, CF_3, *J*=5.9 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 84%) δ 1.11, 1.14, 2.22, 2.23 (all s, 3H, Me), 2.63 (s, 2H, H-4), 3.22 (dd, 1H, C*H*H, *J*=17.7, 3.8 Hz), 3.33 (dd, 1H, CH*H*, *J*=17.7, 11.0 Hz), 4.00 (dd, 1H, H-4′, *J*=11.0, 3.8 Hz), 5.53 (qd, 1H, H-2′, *J*=6.3, 1.9 Hz), 5.57 (d, 1H, H-3′, *J*=1.9 Hz), 7.02 (s, 1H, H-5), 7.03 (dd, 1H, H-8′, *J*=8.3, 1.2 Hz), 7.08 (td, 1H, H-6′, *J*=7.5, 1.2 Hz), 7.25 (ddd, 1H, H-7′, *J*=8.3, 7.3, 1.2 Hz), 7.35 (s, 1H, H-8), 7.46 (dd, 1H, H-5′, *J*=7.8, 1.2 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) (*ct*, 84%) δ 88.1 (d, CF_3, *J*=6.3 Hz), (*tc*, 16%) δ 87.8 (d, CF_3, *J*=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (*tc*+*ct*) δ 19.6 (2C), 19.8 (2C), 27.6, 27.7, 28.1, 28.2, 32.0, 33.6, 35.7, 38.2, 38.3, 41.5, 53.9, 54.2, 70.6 (q, C-2′, $^{2}J_{C,F}$=34.1 Hz), 73.5 (q, C-2′, $^{2}J_{C,F}$=32.5 Hz), 78.5, 80.9, 117.0, 117.2, 122.1 (q, CF_3, $^{1}J_{C,F}$=280.9 Hz), 122.3, 122.9, 123.0, 123.0, 123.0 (q, CF_3, $^{1}J_{C,F}$=283.0 Hz), 125.1 (2C), 125.3, 125.8, 126.5, 128.3, 128.8, 128.9, 129.8, 130.1, 134.0, 134.3, 134.8, 135.0, 139.7, 140.3, 152.0, 152.1, 158.8, 159.0. Anal. Calcd for $C_{24}H_{25}F_3N_2O_3$: C, 64.57; H, 5.64; N, 6.27. Found: C, 64.53; H, 5.70; N, 6.24.

*3.3.3. 6,7-Dimethoxy-3,3-dimethyl-1-[3-nitro-2-(trifluoromethyl)chroman-4-yl]methyl-3,4-dihydroisoquinoline (**5c**).* Yield 0.39 g (81%, 3 h), mp 150–151 °C (decomp.); IR (KBr) 1627, 1605, 1574, 1555, 1513, 1493, 1379, 1360 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 53%) δ 1.13 (s, 3H, Me), 1.17 (s, 3H, Me), 2.59 (AB-system, 2H, H-4, *J*=16.2 Hz), 3.02 (dd, 1H, C*H*H, *J*=16.3, 8.1 Hz), 3.21 (dd, 1H, CH*H*, *J*=16.3, 6.2 Hz), 3.90 (s, 3H, MeO), 3.92 (s, 3H, MeO), 4.24–4.33 (m, 1H, H-4′), 5.32 (qd, 1H, H-2′, *J*=6.4, 4.8 Hz), 5.76 (t, 1H, H-3′, *J*=4.8 Hz), 6.65 (s, 1H, H-5), 6.88 (s, 1H, H-8), 7.00–7.30 (m, 4H, arom.), (*ct*, 47%) δ 1.20 (s, 3H, Me), 1.22 (s, 3H, Me), 2.66 (s, 2H, H-4), 2.78 (dd, 1H, C*H*H, *J*=17.0, 11.8 Hz), 3.31 (dd, 1H, CH*H*, *J*=17.0, 3.0 Hz), 3.88 (s, 3H, MeO), 3.93 (s, 3H, MeO), 4.08 (dd, 1H, H-4′, *J*=11.8, 3.0 Hz), 4.54–4.63 (m, 1H, H-2′), 5.54–5.60 (m, 1H, H-3′), 6.69 (s, 1H, H-5), 6.89 (s, 1H, H-8), 7.00–7.30 (m, 4H, arom.); ^{19}F NMR (376 MHz, $CDCl_3$) (*tc*, 53%) δ 85.0 (d, CF_3, *J*=6.4 Hz), (*ct*, 47%) δ 86.5 (d, CF_3, *J*=5.8 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 86%) δ 1.12 (s, 3H, Me), 1.15 (s, 3H, Me), 2.64 (s, 2H, H-4), 3.24 (dd, 1H, C*H*H, *J*=17.7, 3.9 Hz), 3.34 (dd, 1H, CH*H*, *J*=17.7, 11.0 Hz), 3.76 (s, 3H, MeO), 3.81 (s, 3H, MeO), 4.03 (dd, 1H, H-4′, *J*=11.0, 3.9 Hz), 5.52 (qd, 1H, H-2′, *J*=6.4, 1.8 Hz), 5.56 (br d, 1H, H-3′, *J*=1.8 Hz), 6.87 (s, 1H, H-5), 7.04 (dd, 1H, H-8′, *J*=8.2, 1.2 Hz), 7.09 (td, 1H, H-6′, *J*=7.6, 1.2 Hz), 7.10 (s, 1H, H-8), 7.25 (td, 1H, H-7′, *J*=7.9, 1.5 Hz), 7.45 (dd, 1H, H-5′, *J*=7.9, 1.5 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) (*ct*, 85%) δ 88.2 (d, CF_3, *J*=6.4 Hz), (*tc*, 15%) δ 87.8 (br d, CF_3, *J*=6.0 Hz). Anal. Calcd for $C_{24}H_{25}F_3N_2O_5$: C, 60.25; H, 5.27; N, 5.85. Found: C, 60.26; H, 5.30; N, 5.62.

*3.3.4. 6,7-Dimethoxy-1-[6-methoxy-3-nitro-2-(trifluoromethyl)chroman-4-yl]methyl-3,3-dimethyl-3,4-dihydroisoquinoline (**5d**).* Yield 0.43 (84%, 0.5 h), mp 164–165 °C (decomp.); IR (KBr) 1626, 1607, 1576, 1558, 1515, 1500, 1356 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 55%) δ 1.14 (s, 3H, Me), 1.18 (s, 3H, Me), 2.60 (AB-system, 2H, H-4, *J*=16.1 Hz), 3.00 (dd, 1H, C*H*H, *J*=16.0, 7.7 Hz), 3.18 (dd, 1H, CH*H*, *J*=16.0, 6.4 Hz), 3.74, 3.91, 3.92 (all s, 3H, MeO), 4.26 (br q, 1H, H-4′, *J*=6.1 Hz), 5.28 (qd, 1H, H-2′, *J*=6.5, 4.5 Hz), 5.70 (br t, 1H, H-3′, *J*=4.5 Hz), 6.65 (s, 1H, H-5), 6.71 (d, 1H, H-5′, *J*=2.7 Hz), 6.77 (dd, 1H, H-7′, *J*=8.8, 2.7 Hz), 6.87 (s, 1H, H-8), 6.98 (d, 1H, H-8′, *J*=8.8 Hz), (*ct*, 45%) δ 1.21 (s, 3H, Me), 1.22 (s, 3H, Me), 2.66 (s, 2H, H-4), 2.79 (dd, 1H, C*H*H, *J*=16.8, 12.3 Hz), 3.31 (dd, 1H, CH*H*, *J*=16.8, 3.2 Hz), 3.79, 3.89, 3.93 (all s, 3H, MeO), 4.08 (m, 1H, H-4′), 4.52 (br q, 1H, H-2′, *J*=5.5 Hz), 5.52 (m, 1H, H-3′), 6.69 (s, 1H, H-5), 6.79 (d, 1H, H-5′, *J*=2.7 Hz), 6.83 (dd, 1H, H-7′, *J*=8.8, 2.7 Hz), 6.88 (s, 1H, H-8), 7.00 (d, 1H, H-8′, *J*=8.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) (*tc*, 55%) δ 84.9 (d, CF_3, *J*=6.5 Hz), (*ct*, 45%) δ 86.5 (d, CF_3, *J*=5.8 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 90%) δ 1.11 (s, 3H, Me), 1.16 (s, 3H, Me), 2.64 (s, 2H, H-4), 3.31 (d, 2H, CH_2, *J*=7.3 Hz), 3.74, 3.77, 3.81 (all s, 3H, MeO), 4.01 (t, 1H, H-4′, *J*=7.3 Hz), 5.44 (qd, 1H, H-2′, *J*=6.3, 1.5 Hz), 5.50 (br d, 1H, H-3′, *J*=1.5), 6.82 (dd, 1H, H-7′, *J*=8.9, 3.0 Hz), 6.87 (s, 1H, H-5),

6.96 (d, 1H, H-8′, J=8.9 Hz), 7.02 (d, 1H, H-5′, J=3.0 Hz), 7.10 (s, 1H, H-8); ^{19}F NMR (376 MHz, DMSO-d_6) (*ct*, 89%) δ 88.2 (d, CF_3, J=6.3 Hz), (*tc*, 11%) δ 87.6 (br d, CF_3, J=6.3 Hz). Anal. Calcd for $C_{24}H_{27}F_3N_2O_6$: C, 59.05; H, 5.35; N, 5.51. Found: 58.69; H, 5.10; N, 5.21.

*3.3.5. 1-[6-Bromo-3-nitro-2-(trifluoromethyl)chroman-4-yl]methyl-3,3,6,7-tetramethyl-3,4-dihydroisoquinoline (**5e**).* Yield 0.21 g (39%, 1 h), mp 128–129 °C (decomp.); IR (KBr) 1629, 1557, 1481, 1386, 1369 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 54%) δ 1.16, 1.18, 2.28, 2.29 (all s, 3H, Me), 2.62 (br s, 2H, H-4), 3.05 (m, 1H, C*H*H), 3.25 (m, 1H, CH*H*), 4.27 (br q, 1H, H-4′, J=6.5 Hz), 5.27 (br s, 1H, H-2′), 5.85 (br s, 1H, H-3′), 6.9–7.0 (m, 2H, H-5, H-8′), 7.15–7.40 (m, 3H, H-8, H-5′, H-7′), (*ct*, 46%) δ 1.18, 1.20, 2.28, 2.29 (all s, 3H, Me), 2.66 (br s, 2H, H-4), 2.7–2.9 (m, 1H, C*H*H), 3.3–3.4 (m, 1H, CH*H*), 4.08 (br s, 1H, H-4′), 4.56 (br s, 1H, H-2′), 5.50 (s, 1H, H-3′), 6.9–7.0 (m, 2H, H-5, H-8′), 7.15–7.40 (m, 3H, H-8, H-5′, H-7′); ^{19}F NMR (376 MHz, $CDCl_3$) (*tc*, 54%) δ 85.2 (d, CF_3, J=6.6 Hz), (*ct*, 46%) δ 86.5 (d, CF_3, J=5.8 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 84%) δ 1.12 (br s, 6H, 2Me), 2.22 (s, 3H, Me), 2.23 (s, 3H, Me), 2.63 (AB-system, 2H, H-4, J=16.7 Hz), 3.26 (dd, 1H, C*H*H, J=17.5, 5.0 Hz), 3.33 (dd, 1H, CH*H*, J=17.5, 9.5 Hz), 4.07 (dd, 1H, H-4′, J=9.5, 5.0 Hz), 5.57 (br q, 1H, H-2′, J=6.2 Hz), 5.63 (br s, 1H, H-3′), 7.02 (s, 1H, H-5), 7.02 (d, 1H, H-8′, J=8.7 Hz), 7.36 (s, 1H, H-8), 7.40 (dd, 1H, H-7′, J=8.7, 2.2 Hz), 7.71 (d, 1H, H-5′, J=2.2 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) (*ct*, 84%) δ 88.2 (d, CF_3, J=6.2 Hz), (*tc*, 16%) δ 87.8 (d, CF_3, J=6.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (*tc*+*ct*) δ 19.6 (2C), 19.8 (2C), 27.6, 27.7, 27.9, 28.0, 31.8, 33.3, 35.4, 38.2, 41.2, 54.0, 54.2, 70.6 (q, C-2′, $^2J_{C,F}$=34.0 Hz), 73.4 (q, C-2′, $^2J_{C,F}$=32.9 Hz), 78.3, 80.3, 115.2, 118.8, 118.9, 121.9 (q, CF_3, $^1J_{C,F}$=280.5 Hz), 122.8 (q, CF_3, $^1J_{C,F}$=283.1 Hz), 124.5, 125.0 (2C), 125.2, 125.6, 129.6, 129.8, 130.1, 130.6, 131.3, 131.6, 131.7, 133.9, 134.2, 134.9, 135.1, 139.9, 140.4, 151.0, 151.2, 158.4, 158.7. Anal. Calcd for $C_{24}H_{24}BrF_3N_2O_3$: C, 54.87; H, 4.60; N, 5.33. Found: C, 54.78; H, 4.56; N, 5.23.

*3.3.6. 1-[6-Bromo-3-nitro-2-(trifluoromethyl)chroman-4-yl]methyl-6,7-dimethoxy-3,3-dimethyl-3,4-dihydroisoquinoline (**5f**).* Yield 0.48 g (86%, 1 h), 0.51 g (91%, solvent-free, 60 °C, 15 min), mp 140–141 °C (decomp.); IR (KBr) 1629, 1605, 1575, 1558, 1514, 1482, 1364, 1353 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 56%) δ 1.15 (s, 3H, Me), 1.18 (s, 3H, Me), 2.61 (AB-system, 2H, H-4, J=15.9 Hz), 3.00 (dd, 1H, C*H*H, J=16.3, 8.0 Hz), 3.15 (dd, 1H, CH*H*, J=16.3, 6.3 Hz), 3.93 (s, 6H, MeO), 4.27 (br q, 1H, H-4′, J=6.0 Hz), 5.30 (qd, 1H, H-2′, J=6.4, 4.4 Hz), 5.75 (t, 1H, H-3′, J=4.4 Hz), 6.67 (s, 1H, H-5), 6.89 (s, 1H, H-8), 6.93 (d, 1H, H-8′, J=8.5 Hz), 7.30–7.42 (m, 2H, H-5′, H-7′), (*ct*, 44%) δ 1.19 (s, 3H, Me), 1.21 (s, 3H, Me), 2.65 (s, 2H, H-4), 2.80 (dd, 1H, C*H*H, J=17.2, 11.5 Hz), 3.25 (dd, 1H, CH*H*, J=17.2, 3.2 Hz), 3.90 (s, 3H, MeO), 3.93 (s, 3H, MeO), 4.12 (br d, 1H, H-4′, J=11.5 Hz), 4.56 (br q, 1H, H-2′, J=5.5 Hz), 5.52 (br s, 1H, H-3′), 6.69 (s, 1H, H-5), 6.87 (s, 1H, H-8), 6.95 (d, 1H, H-8′, J=8.5 Hz), 7.30–7.42 (m, 2H, H-5′, H-7′); ^{19}F NMR (376 MHz, $CDCl_3$) (*tc*, 55%) δ 85.1 (d, CF_3, J=6.5 Hz), (*ct*, 45%) δ 86.6 (d, CF_3, J=5.7 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 82%) δ 1.13 (s, 3H, Me), 1.14 (s, 3H, Me), 2.64 (AB-system, 2H, H-4, J=16.0 Hz), 3.2–3.3 (m, 2H, CH_2), 3.77 (s, 3H, MeO), 3.81 (s, 3H, MeO), 4.08 (br dd, 1H, H-4′, J=9.5, 4.8 Hz), 5.57 (br q, 1H, H-2′, J=6.3 Hz), 5.61 (br s, 1H, H-3′), 6.87 (s, 1H, H-5), 7.02 (d, 1H, H-8′, J=8.8 Hz), 7.11 (s, 1H, H-8), 7.41 (dd, 1H, H-7′, J=8.8, 2.3 Hz), 7.68 (d, 1H, H-5′, J=2.3 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) (*ct*, 83%) δ 88.2 (d, CF_3, J=6.2 Hz), (*tc*, 17%) δ 87.7 (br d, CF_3, J=6.2 Hz). Anal. Calcd for $C_{24}H_{24}BrF_3N_2O_5$: C, 51.72; H, 4.34; N, 5.03. Found: C, 51.64; H, 4.32; N, 4.91.

3.4. Compounds 6a–h

*3.4.1. 3,3-Dimethyl-1-[3-nitro-2-(trichloromethyl)chroman-4-yl]methyl-3,4-dihydroisoquinoline (**6a**).* Yield 0.28 g (60%, 12 h), mp 122–123 °C (decomp.); IR (KBr) 1629, 1552, 1484, 1457, 1363 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 83%) δ 1.14 (s, 3H, Me), 1.19 (s, 3H, Me), 2.65 (AB-system, 2H, H-4, J=15.8 Hz), 2.99 (dd, 1H, C*H*H, J=16.5, 8.3 Hz), 3.27 (dd, 1H, CH*H*, J=16.5, 6.3 Hz), 4.36 (dt, 1H, H-4′, J=7.7, 6.0 Hz), 5.38 (d, 1H, H-2′, J=4.9 Hz), 5.99 (t, 1H, H-3′, J=5.2 Hz), 7.04 (td, 1H, H-6′, J=7.5, 1.1 Hz), 7.1–7.4 (m, 7H, arom.), (*ct*, 17%) δ 1.20 (s, 3H, Me), 1.27 (s, 3H, Me), 2.74 (AB-system, 2H, H-4, J=15.5 Hz), 2.82 (dd, 1H, C*H*H, J=16.6, 12.0 Hz), 3.40 (dd, 1H, CH*H*, J=16.6, 3.2 Hz), 3.98 (br dd, 1H, H-4′, J=12.0, 3.0 Hz), 4.61 (d, 1H, H-2′, J=1.6 Hz), 6.08 (br t, 1H, H-3′, J=1.3 Hz), 7.1–7.5 (m, 8H, arom.); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 64%) δ 1.12, 1.20 (both s, 3H, Me), 2.72 (s, 2H, H-4), 3.25 (dd, 1H, C*H*H, J=17.9, 3.2 Hz), 3.52 (dd, 1H, CH*H*, J=17.9, 11.5 Hz), 3.95 (dd, 1H, H-4′, J=11.5, 3.2 Hz), 5.44 (d, 1H, H-2′, J=1.6 Hz), 6.03 (br s, 1H, H-3′), 7.0–7.6 (m, 8H, arom.), (*tc*, 36%) δ 1.10 (s, 3H, Me), 1.20 (s, 3H, Me), 2.70 (s, 2H, H-4), 2.81 (dd, 1H, C*H*H, J=17.7, 9.9 Hz), 3.60 (dd, 1H, CH*H*, J=17.7, 4.8 Hz), 4.22 (dt, 1H, H-4′, J=10.0, 4.8 Hz), 5.54 (d, 1H, H-2′, J=3.5 Hz), 6.37 (dd, 1H, H-3′, J=5.3, 3.5 Hz), 7.1–7.7 (m, 8H, arom.); ^{13}C NMR (100 MHz, $CDCl_3$) (*tc*) δ 27.7, 28.1, 31.9, 35.9, 38.7, 54.0, 85.6, 86.1, 98.6, 117.7, 123.5, 124.1, 125.2, 126.5, 126.9, 127.9, 128.4, 128.8, 130.7, 136.6, 153.3, 158.9. Anal. Calcd for $C_{22}H_{21}Cl_3N_2O_3$: C, 56.49; H, 4.53; N, 5.99. Found: C, 56.53; H, 4.31; N, 5.92.

*3.4.2. 3,3,6,7-Tetramethyl-1-[3-nitro-2-(trichloromethyl)chroman-4-yl]methyl-3,4-dihydroisoquinoline (**6b**).* Yield 0.39 g (78%, 10 h), mp 136–137 °C; IR (KBr) 1625, 1613, 1588, 1544, 1484, 1458, 1357 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 84%) δ 1.1–1.3 (br s, 6H, 2 Me), 2.28 (s, 6H, 2 Me), 2.6 (m, 2H, H-4), 3.0 (m, 1H, C*H*H), 3.2 (m, 1H, CH*H*), 4.4 (m, 1H, H-4′), 5.4 (m, 1H, H-2′), 6.0 (m, 1H, H-3′), 6.9–7.3 (m, 6H, arom.), (*ct*, 16%) δ 1.1–1.3 (br s, 6H, 2 Me), 2.28 (br s, 6H, 2 Me), 2.7 (br s, 2H, H-4), 2.8 (m, 1H, C*H*H), 3.4 (m, 1H, CH*H*), 3.97 (d, 1H, H-4′, J=11.5 Hz), 4.6 (m, 1H, H-2′), 6.1 (m, 1H, H-3′), 6.9–7.3 (m, 6H, arom.); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 65%) δ 1.09, 1.19, 2.22, 2.23 (all s, 3H, Me), 2.63 (s, 2H, H-4), 3.19 (dd, 1H, C*H*H, J=17.9, 3.2 Hz), 3.51 (dd, 1H, CH*H*, J=17.9, 11.6 Hz), 3.94 (dd, 1H, H-4′, J=11.6, 3.3 Hz), 5.42 (d, 1H, H-2′, J=1.6 Hz), 6.01 (br s, 1H, H-3′), 7.02 (s, 1H, H-5), 7.38 (s, 1H, H-8), 7.1–7.5 (m, 4H, arom.), (*tc*, 35%) δ 1.08, 1.18, 2.23, 2.25 (all s, 3H, Me), 2.61 (s, 2H, H-4), 2.79 (dd, 1H, C*H*H, J=17.5, 9.9 Hz), 3.54 (dd, 1H, CH*H*, J=17.5, 4.7 Hz), 4.20 (dt, 1H, H-4′, J=9.9, 4.7 Hz), 5.52 (d, 1H, H-2′, J=2.5 Hz), 6.38 (s, 1H, H-3′), 7.0–7.5 (m, 6H, arom.). Anal. Calcd for $C_{24}H_{25}Cl_3N_2O_3$: C, 58.14; H, 5.08; N, 5.65. Found: C, 58.14; H, 5.13; N, 5.67.

*3.4.3. 6,7-Dimethoxy-3,3-dimethyl-1-[3-nitro-2-(trichloromethyl)chroman-4-yl]methyl-3,4-dihydroisoquinoline (**6c**).* Yield 0.38 g (71%, 5 h), mp 123–124 °C (decomp.); IR (KBr) 1621, 1606, 1572, 1554, 1512, 1492, 1455, 1359, 1340 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 84%) δ 1.14 (br s, 3H, Me), 1.20 (br s, 3H, Me), 2.58 (m, 2H, H-4), 2.95 (br s, 1H, C*H*H), 3.20 (br s, 1H, CH*H*), 3.91 (s, 3H, MeO), 3.92 (s, 3H, MeO), 4.36 (br s, 1H, H-4′), 5.47 (br s, 1H, H-2′), 5.87 (br s, 1H, H-3′), 6.64 (s, 1H, H-5), 6.86 (s, 1H, H-8), 7.0–7.3 (m, 4H, arom.), (*ct*, 16%) δ 1.21 (br s, 3H, Me), 1.26 (br s, 3H, Me), 2.67 (br s, 2H, H-4), 2.9 (br s, 1H, C*H*H), 3.3 (br s, 1H, CH*H*), 3.90 (s, 3H, MeO), 3.94 (s, 3H, MeO), 4.0 (m, 1H, H-4′), 4.61 (br s, 1H, H-2′), 6.08 (br s, 1H, H-3′), 6.70 (s, 1H, H-5), 6.93 (s, 1H, H-8), 7.0–7.3 (m, 4H, arom.). Anal. Calcd for $C_{24}H_{25}Cl_3N_2O_5$: C, 54.61; H, 4.77; N, 5.31. Found: C, 54.68; H, 4.64; N, 5.42.

*3.4.4. 6,7-Dimethoxy-1-[6-methoxy-3-nitro-2-(trichloromethyl)chroman-4-yl]methyl-3,3-dimethyl-3,4-dihydroisoquinoline (**6d**).* Yield 0.35 g (62%, 3 h), mp 122–124 °C (decomp.); IR (KBr) 1632, 1617, 1604, 1558, 1515, 1500, 1464, 1357 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 86%) δ 1.14 (s, 3H, Me), 1.20 (s, 3H, Me), 2.58 (AB-system, 2H, H-4, J=15.7 Hz), 2.91 (br dd, 1H, C*H*H, J=16.0, 8.2 Hz), 3.17 (br dd, 1H, CH*H*, J=16.0, 6.5 Hz), 3.75 (s, 3H, MeO), 3.91 (s, 6H, 2MeO), 4.32 (m, 1H, H-4′), 5.37 (d, 1H, H-2′, J=4.7 Hz), 5.87 (br t, 1H, H-3′, J=5.0 Hz), 6.64 (s, 1H, H-5), 6.70 (d, 1H, H-5′,

J=2.9 Hz), 6.77 (dd, 1H, H-7′, *J*=8.8, 2.8 Hz), 6.86 (s, 1H, H-8), 7.04 (d, 1H, H-8′, *J*=8.8 Hz), (*ct*, 14%) *δ* 1.20 (s, 3H, Me), 1.25 (s, 3H, Me), 2.66 (AB-system, 2H, H-4, *J*=15.5 Hz), 2.77–2.84 (m, 1H, C*H*H), 3.30–3.35 (m, 1H, CH*H*), 3.80 (s, 3H, MeO), 3.90 (s, 3H, MeO), 3.93 (s, 3H, MeO), 4.01 (br dd, 1H, H-4′, *J*=11.0, 3.0 Hz), 4.55 (br s, 1H, H-2′), 6.03 (br s, 1H, H-3′), 6.70 (s, 1H, H-5), 6.80 (d, 1H, H-5′, *J*=2.8 Hz), 6.86 (dd, 1H, H-7′, *J*=8.8, 2.8 Hz), 6.91 (s, 1H, H-8), 7.08 (d, 1H, H-8′, *J*=8.8 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 70%) *δ* 1.10 (s, 3H, Me), 1.20 (s, 3H, Me), 2.64 (br s, 2H, H-4), 3.27 (dd, 1H, C*H*H, *J*=18.0, 3.2 Hz), 3.50 (br dd, 1H, CH*H*, *J*=18.0, 11.0 Hz), 3.75, 3.78, 3.81 (all s, 3H, MeO), 3.94 (br dd, 1H, H-4′, *J*=11.0, 3.0 Hz), 5.31 (d, 1H, H-2′, *J*=1.5 Hz), 5.95 (br s, 1H, H-3′), 6.84 (dd, 1H, H-7′, *J*=8.9, 2.8 Hz), 6.87 (s, 1H, H-5), 6.99 (d, 1H, H-8′, *J*=8.9 Hz), 7.03 (d, 1H, H-5′, *J*=2.8 Hz), 7.15 (s, 1H, H-8), (***t***c, 30%) *δ* 1.08 (s, 3H, Me), 1.19 (s, 3H, Me), 2.61 (br s, 2H, H-4), 2.80 (dd, 1H, C*H*H, *J*=17.9, 9.3 Hz), 3.50 (m, 1H, CH*H*), 3.74, 3.81, 3.82 (all s, 3H, MeO), 4.14 (dt, 1H, H-4′, *J*=9.3, 4.8 Hz), 5.39 (m, 1H, H-2′), 6.30 (m, 1H, H-3′), 6.8–7.2 (m, 5H, arom.). Anal. Calcd for $C_{24}H_{27}Cl_3N_2O_6$: C, 53.83; H, 4.88; N, 5.02. Found: C, 53.75; H, 4.70; N, 5.00.

*3.4.5. 1-[6-Bromo-3-nitro-2-(trichloromethyl)chroman-4-yl]methyl-3,3,6,7-tetramethyl-3,4-dihydroisoquinoline (**6e**).* Yield 0.30 g (52%, 3 h), 62% [benzene, reflux, Et_3N (5 mol %), 15 min], mp 159–160 °C (decomp.); IR (KBr) 1624, 1544, 1479, 1365, 1356 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 84%) *δ* 1.15, 1.18, 2.27, 2.29 (all s, 3H, Me), 2.59 (AB-system, 2H, H-4, *J*=15.9 Hz), 2.94 (br dd, 1H, CH*H*, *J*=16.5, 7.6 Hz), 3.18 (br dd, 1H, CH*H*, *J*=16.5, 6.8 Hz), 4.34 (br q, 1H, H-4′, *J*=6.5 Hz), 5.38 (d, 1H, H-2′, *J*=4.2 Hz), 5.96 (br t, 1H, H-3′, *J*=5.0 Hz), 6.92 (s, 1H, H-5), 7.00 (d, 1H, H-8′, *J*=8.5 Hz), 7.15 (s, 1H, H-8), 7.34 (d, 1H, H-5′, *J*=2.3 Hz), 7.36 (dd, 1H, H-7′, *J*=8.5, 2.3 Hz), (*ct*, 16%) *δ* 1.20, 1.22, 2.27, 2.29 (all s, 3H, Me), 2.66 (br s, 2H, H-4), 2.94 (m, 1H, C*H*H), 3.18 (m, 1H, CH*H*), 4.03 (m, 1H, H-4′), 4.59 (br s, 1H, H-2′), 6.01 (br s, 1H, H-3′), 6.97 (s, 1H, H-5), 7.02 (d, 1H, H-8′, *J*=8.5 Hz), 7.18 (s, 1H, H-8), 7.32–7.42 (m, 2H, H-5′, H-7′); ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 65%) *δ* 1.12, 1.17, 2.23, 2.24 (all s, 3H, Me), 2.62 (m, 2H, H-4), 3.25 (dd, 1H, *CH*H, *J*=17.7, 3.7 Hz), 3.52 (br dd, 1H, *CH*H, *J*=17.5, 5.5 Hz), 4.00 (br dd, 1H, H-4′, *J*=10.5, 3.5 Hz), 5.47 (d, 1H, H-2′, *J*=1.5 Hz), 6.04 (br s, 1H, H-3′), 7.03 (s, 1H, H-5), 7.04 (d, 1H, H-8′, *J*=8.8 Hz), 7.42 (dd, 1H, H-7′, *J*=8.8, 2.3 Hz), 7.50 (s, 1H, H-8), 7.71 (br s, 1H, H-5′), (***t***c, 35%) *δ* 1.10, 1.17, 2.24, 2.25 (all s, 3H, Me), 2.64 (br s, 2H, H-4), 2.80 (m, 1H, C*H*H), 3.52 (m, 1H, CH*H*), 4.20 (br dt, 1H, H-4′, *J*=9.0, 5.0 Hz), 5.60–5.65 (br s, 1H, H-2′), 6.36 (br s, 1H, H-3′), 7.0–7.7 (m, 5H, arom.). Anal. Calcd for $C_{24}H_{24}BrCl_3N_2O_3$: C, 50.16; H, 4.21; N, 4.87. Found: C, 50.18; H, 4.11; N, 4.76.

*3.4.6. 1-[6-Bromo-3-nitro-2-(trichloromethyl)chroman-4-yl]methyl-6,7-dimethoxy-3,3-dimethyl-3,4-dihydroisoquinoline (**6f**).* Yield 0.35 g (58%, 5 h), mp 120–121 °C (decomp.); IR (KBr) 1630, 1617, 1606, 1576, 1555, 1514, 1482, 1465, 1354 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (*tc*, 85%) *δ* 1.15 (s, 3H, Me), 1.18 (s, 3H, Me), 2.59 (AB-system, 2H, H-4, *J*=15.9 Hz), 2.91 (m, 1H, C*H*H), 3.11 (m, 1H, CH*H*), 3.93 (s, 3H, MeO), 3.94 (s, 3H, MeO), 4.34 (m, 1H, H-4′), 5.46 (m, 1H, H-2′), 5.83 (m, 1H, H-3′), 6.66 (s, 1H, H-5), 6.86 (s, 1H, H-8), 6.99 (d, 1H, H-8′, *J*=8.5 Hz), 7.27 (m, 1H, H-5′), 7.36 (dd, 1H, H-7′, *J*=8.5, 2.3 Hz), (*ct*, 15%) *δ* 1.21 (s, 3H, Me), 1.23 (s, 3H, Me), 2.66 (br s, 2H, H-4), 2.80 (m, 1H, C*H*H), 3.26 (m, 1H, CH*H*), 3.92 (s, 3H, MeO), 3.94 (s, 3H, MeO), 4.05 (dd, 1H, H-4′, *J*=10.7, 2.6 Hz), 4.58 (m, 1H, H-2′), 6.03 (m, 1H, H-3′), 6.70 (s, 1H, H-5), 6.90 (s, 1H, H-8), 7.03 (d, 1H, H-8′, *J*=8.6 Hz), 7.27 (m, 1H, H-5′), 7.40 (br d, 1H, H-7′, *J*=8.6 Hz). Anal. Calcd for $C_{24}H_{24}BrCl_3N_2O_5$: C, 47.51; H, 3.99; N, 4.62. Found: C, 47.32; H, 3.99; N, 4.50.

*3.4.7. 3,3-Dimethyl-1-(3-nitro-2-phenylchroman-4-yl)methyl-3,4-dihydroisoquinoline (**6g**).* Yield 0.27 g (64%, 8 h), mp 143–144 °C (decomp.); IR (KBr) 1628, 1585, 1554, 1488, 1454, 1371, 1360 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 88%) *δ* 1.10, 1.12 (both s, 3H, Me), 2.72 (AB-system, 2H, H-4, *J*=16.0 Hz), 3.38 (ABX-system, 2H, CH_2, *J*=17.3, 10.1, 4.6 Hz), 4.02 (dd, 1H, H-4′, *J*=10.1, 4.6 Hz), 5.39 (d, 1H, H-2′, *J*=2.2 Hz), 5.70 (d, 1H, H-3′, *J*=2.2 Hz), 7.0–7.7 (m, 13H, arom.), (*tc*, 12%) *δ* 0.99, 1.06 (both s, 3H, Me), 2.63 (s, 2H, H-4), 3.03–3.16 (m, 2H, CH_2), 4.02 (m, 1H, H-4′), 5.92 (t, 1H, H-3′, *J*=4.8 Hz), 5.99 (d, 1H, H-2′, *J*=4.6 Hz), 6.9–7.6 (m, 13H, arom.). Anal. Calcd for $C_{27}H_{26}N_2O_3$: C, 76.03; H, 6.14; N, 6.57. Found: C, 76.11; H, 6.22; N, 6.47.

*3.4.8. 6,7-Dimethoxy-3,3-dimethyl-1-(3-nitro-2-phenylchroman-4-yl)methyl-3,4-dihydroisoquinoline (**6h**).* Yield 0.44 g (91%, 3 h), mp 183–185 °C (decomp.); IR (KBr) 1624, 1606, 1583, 1574, 1553, 1516, 1490, 1453, 1355 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) (*ct*, 90%) *δ* 1.08, 1.13 (both s, 3H, Me), 2.63 (AB-system, 2H, H-4, *J*=16.4 Hz), 3.27–3.44 (m, 2H, CH_2), 3.80 (s, 3H, MeO), 3.81 (s, 3H, MeO), 4.02 (dd, 1H, H-4′, *J*=10.5, 4.5 Hz), 5.36 (d, 1H, H-2′, *J*=2.3 Hz), 5.71 (t, 1H, H-3′, *J*=2.3 Hz), 6.9–7.5 (m, 11H, arom.). Anal. Calcd for $C_{29}H_{30}N_2O_5$: C, 71.59; H, 6.21; N, 5.76. Found: C, 71.54; H, 6.19; N, 5.72.

3.5. Compounds 8a–h

A mixture of the corresponding chromene **1** (1.0 mmol), hydrochloride **7** (1.0 mmol) and triethylamine (0.12 g, 1.2 mmol) was refluxed in isobutanol (2 mL) for 3 h. After that, the mixture was concentrated under reduced pressure and the solid formed was washed with water, filtered, dried, and recrystallized from dichloromethane/hexane to give compound **8** as a colourless powder.

*3.5.1. 11,12-Dimethoxy-8-methyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**8a**).* Yield 0.32 g (78%), mp 175–176 °C; IR (KBr) 1612, 1561, 1536, 1492 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (trans, 53%) *δ* 1.26 (d, 3H, Me, *J*=6.7 Hz), 2.75 (d, 1H, H-9′, *J*=15.5 Hz), 3.40 (dd, 1H, H-9″, *J*=15.3, 6.0 Hz), 3.91, 3.96 (all s, 3H, MeO), 4.50 (qdd, 1H, H-8, *J*=6.7, 6.0, 1.7 Hz), 5.80 (q, 1H, H-6, $^3J_{H,F}$=6.1 Hz), 6.66 (s, 1H, H-10/14), 6.71 (s, 1H, H-14/10), 6.99–7.04 (m, 2H, H-2, H-4), 7.08 (s, 1H, H-13), 7.09 (td, 1H, H-3, *J*=7.6, 2.1 Hz), 7.41 (dd, 1H, H-1, *J*=7.7, 1.6 Hz), (cis, 47%) *δ* 1.21 (d, 3H, Me, *J*=6.4 Hz), 2.71 (dd, 1H, H-9′, *J*=15.5, 1.3 Hz), 3.29 (dd, 1H, H-9″, *J*=15.5, 5.5 Hz), 3.92, 3.97 (all s, 3H, MeO), 4.41 (qdd, 1H, H-8, *J*=6.4, 5.5, 1.3 Hz), 5.65 (q, 1H, H-6, $^3J_{H,F}$=6.5 Hz), 6.65 (s, 1H, H-10/14), 6.75 (s, 1H, H-14/10), 6.99–7.04 (m, 2H, H-2, H-4), 7.10 (s, 1H, H-13), 7.10 (ddd, 1H, H-3, *J*=8.3, 7.0, 1.6 Hz), 7.43 (dd, 1H, H-1, *J*=7.7, 1.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) (trans, 53%) *δ* 83.0 (d, CF_3, $^3J_{F,H}$=6.1 Hz), (cis, 47%) *δ* 84.4 (d, CF_3, $^3J_{F,H}$=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) (cis+trans) *δ* 19.5 (q, Me, $^6J_{C,F}$=2.6 Hz), 20.3, 34.6, 35.9, 47.5, 48.6 (unres. q), 56.0, 56.1 (2C), 69.9 (q, C-6, $^2J_{C,F}$=34.4 Hz), 70.6 (q, C-6, $^2J_{C,F}$=33.9 Hz), 96.5, 97.7, 106.0, 106.2, 112.1, 112.2, 114.8, 115.2, 115.9, 116.0, 117.7, 117.9, 120.1, 120.6, 120.7, 120.8, 121.2, 122.2 (2C), 122.3, 122.6 (2C), 122.9 (q, CF_3, $^1J_{C,F}$=286.7 Hz), 123.3 (q, CF_3, $^1J_{C,F}$=288.0 Hz), 126.7, 126.8, 132.2, 132.5, 148.2 (2C), 148.3 (2C), 149.7, 149.8; CMS (EI, 70 eV) *m*/*z* 415 $[M]^+$ (27), 346 $[M-CF_3]^+$ (100), 330 $[M-CF_3-CH_4]^+$ (30), 173 (38), 129 (17), 123 (18). Anal. Calcd for $C_{23}H_{20}F_3NO_3$: C, 66.50; H, 4.85; N, 3.37. Found: C, 66.56; H, 4.78; N, 3.32.

*3.5.2. 2,11,12-Trimethoxy-8-methyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**8b**).* Yield 0.20 g (44%), mp 185–186 °C; IR (KBr) 1622, 1614, 1564, 1534, 1510, 1490 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (trans, 86%) *δ* 1.25 (d, 3H, Me, *J*=6.6 Hz), 2.71 (dd, 1H, H-9′, *J*=15.4, 1.4 Hz), 3.39 (dd, 1H, H-9″, *J*=15.4, 5.9 Hz), 3.82, 3.91, 3.96 (all s, 3H, MeO), 4.50 (dqd, 1H, H-8, *J*=6.6, 5.9, 1.4 Hz), 5.74 (q, 1H, H-6, $^3J_{H,F}$=6.1 Hz), 6.62 (dd, 1H, H-3, *J*=8.8, 2.9 Hz), 6.64 (s, 1H, H-10/14), 6.71 (s, 1H, H-14/10), 6.92 (d, 1H, H-4, *J*=8.8 Hz), 6.95 (d, 1H, H-1, *J*=2.9 Hz), 7.08 (s, 1H, H-13); (cis, 14%) *δ* 1.21 (d, 3H, Me, *J*=6.4 Hz), 2.75 (d, 1H, H-9′, *J*=15.5 Hz), 3.29 (dd, 1H, H-9″, *J*=15.5, 5.7 Hz), 3.83, 3.92, 3.97 (all s, 3H, MeO), 4.40 (m, 1H, H-8), 5.59 (q, 1H, H-6, $^3J_{H,F}$=6.5 Hz), 6.63 (s, 1H, H-10/

14), 6.64 (dd, 1H, H-3, J=8.8, 2.9 Hz), 6.75 (s, 1H, H-14/10), 6.92 (d, 1H, H-4, J=8.8 Hz), 6.98 (d, 1H, H-1, J=2.9 Hz), 7.10 (s, 1H, H-13); ^{19}F NMR (376 MHz, $CDCl_3$) (trans, 86%) δ 83.3 (d, CF_3, $^3J_{F,H}$=6.1 Hz), (cis, 14%) δ 84.6 (d, CF_3, $^3J_{F,H}$=6.5 Hz). Anal. Calcd for $C_{24}H_{22}F_3NO_4$: C, 64.71; H, 4.98; N, 3.14. Found: C, 64.93; H, 4.85; N, 3.00.

*3.5.3. 2-Bromo-11,12-dimethoxy-8-methyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**8c**).* Yield 0.24 g (48%), mp 185–186 °C; IR (KBr) 1605, 1556, 1534, 1495 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (trans, 78%) δ 1.26 (d, 3H, Me, J=6.7 Hz), 2.71 (dd, 1H, H-9′, J=15.5, 1.6 Hz), 3.39 (dd, 1H, H-9″, J=15.5, 6.0 Hz), 3.91, 3.95 (all s, 3H, MeO), 4.49 (qdd, 1H, H-8, J=6.7, 6.0, 1.6 Hz), 5.79 (q, 1H, H-6, $^3J_{H,F}$=6.2 Hz), 6.64 (s, 1H, H-10/14), 6.71 (s, 1H, H-14/10), 6.87 (d, 1H, H-4, J=8.5 Hz), 7.06 (s, 1H, H-13), 7.16 (dd, 1H, H-3, J=8.5, 2.3 Hz), 7.52 (d, 1H, H-1, J=2.3 Hz); (cis, 22%) δ 1.21 (d, 3H, Me, J=6.6 Hz), 2.75 (dd, 1H, H-9′, J=15.2 Hz), 3.28 (dd, 1H, H-9″, J=15.3, 5.3 Hz), 3.92, 3.96 (all s, 3H, MeO), 4.40 (qdd, 1H, H-8, J=6.6, 5.3, 1.7 Hz), 5.65 (q, 1H, H-6, $^3J_{H,F}$=6.4 Hz), 6.62 (s, 1H, H-10/14), 6.74 (s, 1H, H-14/10), 6.89 (d, 1H, H-4, J=8.5 Hz), 7.08 (s, 1H, H-13), 7.17 (dd, 1H, H-3, J=8.5, 2.4 Hz), 7.54 (d, 1H, H-1, J=2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) (trans, 78%) δ 83.1 (d, CF_3, $^3J_{F,H}$=6.2 Hz), (cis, 22%) δ 84.4 (d, CF_3, $^3J_{F,H}$=6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) (trans) δ 20.4 (Me), 34.6 (C-9), 48.8 (q, C-8, $^5J_{C,F}$=1.8 Hz), 56.1 (2MeO), 70.7 (q, C-6, $^2J_{C,F}$=34.2 Hz), 96.6 (C-14), 106.2 (C-13), 112.3 (C-10), 115.0 (C-14b), 115.1 (C-6a), 116.8 (C-14a), 117.7 (C-4), 120.6 (C-13a), 120.8 (C-9a), 122.2 (C-2), 123.0 (q, CF_3, $^1J_{C,F}$=287.9 Hz), 125.0 (C-1), 129.2 (C-3), 132.5 (C-13b), 148.5 (C-11), 148.5 (C-12), 148.8 (C-4a), (cis) δ 19.5 (q, Me, $^6J_{C,F}$=2.9 Hz), 35.9 (C-9), 47.7 (C-8), 56.0 (MeO), 56.1 (MeO), 70.0 (q, C-6, $^2J_{C,F}$=34.6 Hz), 97.8 (C-14), 106.4 (C-13), 112.4 (C-10), 115.1 (C-14b), 115.5 (C-6a), 117.0 (C-14a), 117.7 (C-4), 121.0 (C-13a), 122.2 (C-9a), 122.8 (C-2), 122.8 (q, CF_3, $^1J_{C,F}$=286.7 Hz), 125.1 (C-1), 129.2 (C-3), 132.8 (C-13b), 148.4 (C-11), 148.5 (C-12), 148.7 (C-4a). Anal. Calcd for $C_{23}H_{19}BrF_3NO_3$: C, 55.89; H, 3.87; N, 2.83. Found: C, 56.01; H, 4.08; N, 2.82.

*3.5.4. 2-Bromo-14-(3,4-dimethoxyphenyl)-11,12-dimethoxy-8-methyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**8d**).* Yield 0.32 g (51%), mp 216–217 °C; IR (KBr) 1602, 1576, 1544, 1515, 1482, 1465 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (trans, 87%) δ 1.28 (br s, 3H, Me), 2.70 (d, 1H, H-9′, J=15.6 Hz), 3.35 (s, 3H, MeO), 3.44 (dd, 1H, H-9″, J=15.6, 5.5 Hz), 3.87 (s, 6H, 2 MeO), 3.96 (s, 3H, MeO), 4.54 (br quint, 1H, H-8, J=6.0 Hz), 5.80 (br q, 1H, H-6, $^3J_{H,F}$=5.7 Hz), 6.55 (s, 1H, H-13/10), 6.67 (s, 1H, H-10/13), 6.8–7.1 (m, 6H, arom.), (cis, 13%) δ 1.11 (br s, 3H, Me), 2.7 (m, 1H, H-9′), 3.3 (m, 1H, H-9″), 3.4–4.0 (all s, 12H, 4 MeO), 4.44 (br s, 1H, H-8), 5.67 (q, 1H, H-6, $^3J_{H,F}$=5.4 Hz), 6.6–7.2 (m, 8H, arom.); ^{19}F NMR (376 MHz, $CDCl_3$) (trans, rotamers 1:1, 87%) δ 83.7, 83.8 (both d, CF_3, $^3J_{F,H}$=5.7 Hz), (cis, 13%) δ 84.7 (d, CF_3, $^3J_{F,H}$=5.4 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) (trans, rotamers 1:1, 83%) δ 85.7 (t, CF_3, $^3J_{F,H}$=5.7 Hz), (cis, 17%) δ 86.6 (d, CF_3, $^3J_{F,H}$=7.0 Hz). Anal. Calcd for $C_{31}H_{27}BrF_3NO_5$: C, 59.06; H, 4.32; N, 2.22. Found: C, 58.91; H, 3.98; N, 2.25.

*3.5.5. 8,8-Dimethyl-14-phenyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**8e**).* Yield 0.14 g (39%), mp 180–181 °C; IR (KBr) 1605, 1531, 1494 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38, 1.87 (all s, 3H, Me), 2.76 (d, 1H, H-9′, J=15.1 Hz), 3.27 (d, 1H, H-9″, J=15.1 Hz), 6.25 (q, 1H, H-6, $^3J_{H,F}$=6.2 Hz), 6.66 (ddd, 1H, H-2, J=7.9, 6.5, 2.2 Hz), 6.80 (d, 1H, H-13/1, J=7.4 Hz), 6.82 (d, 1H, H-1/13, J=7.5 Hz), 6.89 (t, 1H, H-12/4, J=7.4 Hz), 6.96 (dd, 1H, H-4/12, J=8.2. 1.8 Hz), 6.98 (td, 1H, H-3/11, J=7.9, 1.4 Hz), 7.04 (td, 1H, H-11/3, J=7.3, 1.2 Hz), 7.12 (d, 1H, H-10, J=7.3 Hz), 7.0–7.9 (m, 5H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.9 (d, CF_3, $^3J_{F,H}$=6.2 Hz). Anal. Calcd for $C_{28}H_{22}F_3NO$: C, 75.49; H, 4.98; N, 3.14. Found: C, 75.40; H, 4.81; N, 3.12.

*3.5.6. 8,8,11,12-Tetramethyl-14-phenyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**8f**).* Yield 0.19 g (39%), mp 223–224 °C; IR (KBr) 1630, 1605, 1587, 1530, 1496 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37, 1.85, 1.88, 2.16 (all s, 3H, Me), 2.69 (d, 1H, H-9′, J=15.3 Hz), 3.19 (d, 1H, H-9″, J=15.3 Hz), 6.24 (q, 1H, H-6, $^3J_{H,F}$=6.2 Hz), 6.53 (s, 1H, H-13), 6.66 (ddd, 1H, H-2, J=7.8, 6.6, 2.2 Hz), 6.86 (dd, 1H, H-1, J=7.8, 0.9 Hz), 6.87 (s, 1H, H-10), 6.95 (dd, 1H, H-4, J=8.2, 1.8 Hz), 6.98 (td, 1H, H-3, J=7.8, 1.2 Hz), 7.0–7.9 (m, 5H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.8 (d, CF_3, $^3J_{F,H}$=6.2 Hz). Anal. Calcd for $C_{30}H_{26}F_3NO$: C, 76.09; H, 5.53; N, 2.96. Found: C, 75.94; H, 5.36; N, 2.82.

*3.5.7. 2-Bromo-8,8,11,12-tetramethyl-14-phenyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**8g**).* Yield 0.21 g (38%), mp 212–213 °C; IR (KBr) 1601, 1581, 1528, 1492 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36, 1.84, 1.89, 2.16 (all s, 3H, Me), 2.68 (d, 1H, H-9′, J=15.2 Hz), 3.19 (d, 1H, H-9″, J=15.2 Hz), 6.23 (q, 1H, H-6, $^3J_{H,F}$=6.1 Hz), 6.59 (s, 1H, H-13/10), 6.82 (d, 1H, H-4, J=8.4 Hz), 6.88 (s, 1H, H-10/13), 6.91 (d, 1H, H-1, J=2.4 Hz), 7.05 (dd, 1H, H-3, J=8.4, 2.4 Hz), 6.9–7.9 (m, 5H, Ph); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.31, 1.76, 1.81, 2.12 (all s, 3H, Me), 2.84 (d, 1H, H-9′, J=15.7 Hz), 3.11 (d, 1H, H-9″, J=15.7 Hz), 6.50 (s, 1H, H-13), 6.76 (d, 1H, H-1, J=2.4 Hz), 6.77 (q, 1H, H-6, $^3J_{H,F}$=6.4 Hz), 6.96 (d, 1H, H-4, J=8.5 Hz), 6.97 (s, 1H, H-10), 7.15 (dd, 1H, H-3, J=8.5, 2.4 Hz), 7.0–7.9 (m, 5H, Ph); ^{19}F NMR (376 MHz, DMSO-d_6) δ 88.9 (d, CF_3, $^3J_{F,H}$=6.4 Hz). Anal. Calcd for $C_{30}H_{25}BrF_3NO$: C, 65.23; H, 4.65; N, 2.54. Found: C, 65.13; H, 4.56; N, 2.48.

*3.5.8. 2-Bromo-11,12-dibutoxy-8,8-dimethyl-14-phenyl-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**8h**).* Yield 0.15 g (23%), mp 129–130 °C; IR (KBr) 1601, 1573, 1548, 1513, 1491, 1466 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91, 0.96 (both t, 3H, Me, J=7.4 Hz), 1.3–1.6 (m, 6H, 3 CH_2), 1.38 (s, 3H, Me), 1.76 (m, 2H, CH_2), 1.83 (s, 3H, Me), 2.65 (d, 1H, H-9′, J=15.1 Hz), 3.18 (d, 1H, H-9″, J=15.1 Hz), 3.21 (m, 1H, OC*H*H), 3.37 (m, 1H, OCH*H*), 3.95 (m, 2H, OCH_2), 6.22 (q, 1H, H-6, $^3J_{H,F}$=6.0 Hz), 6.45 (s, 1H, H-13/10), 6.62 (s, 1H, H-10/13), 6.82 (d, 1H, H-4, J=8.5 Hz), 6.89 (d, 1H, H-1, J=2.2 Hz), 7.06 (dd, 1H, H-3, J=8.5, 2.2 Hz), 7.0–7.8 (m, 5H, Ph); ^{19}F NMR (376 MHz, $CDCl_3$) δ 86.8 (d, CF_3, $^3J_{F,H}$=6.0 Hz). Anal. Calcd for $C_{35}H_{35}BrF_3NO_3$: C, 64.67; H, 5.58; N, 2.09. Found: C, 64.79; H, 5.54; N, 1.98.

3.6. General procedure for the synthesis of compounds 10a–f

A mixture of the corresponding chromene **1** (1.0 mmol) and dihydropapaverine **9** (R=Me) (0.34 g, 1.0 mmol) or drotaverine **9** (R=Et) (0.40 g, 1.0 mmol) was refluxed in isobutanol (2 mL) for 45 min. After that, the mixture was concentrated under reduced pressure and the solid formed was recrystallized from isobutanol/hexane (2:1) to give compound **10** as a colourless powder.

*3.6.1. 14-(3′,4′-Dimethoxyphenyl)-11,12-dimethoxy-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**10a**).* Yield 0.42 g (78%), mp 183–184 °C; IR (KBr) 1610, 1578, 1542, 1515, 1505, 1485 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.05 (t, 2H, H-9, J=5.9 Hz), 3.36, 3.86, 3.95 (all s, 3H, MeO), 3.7–4.0 (m, 4H, MeO, H-8′), 4.07 (dt, 1H, H-8″, J=12.2, 5.9 Hz), 5.75 (q, 1H, H-6, $^3J_{H,F}$=6.2 Hz), 6.57 (s, 1H, H-13), 6.69 (s, 1H, H-10), 6.72 (ddd, 1H, H-2, J=8.0, 7.0, 2.0 Hz), 6.92 (d, 1H, H-1, J=7.7 Hz), 6.98 (dd, 1H, H-4, J=8.0, 1.5 Hz), 7.00 (td, 1H, H-3, J=7.5, 1.5 Hz), 6.8–7.2 (m, 3H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$) δ 83.4 (br d, CF_3, J=6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 42.0, 55.2, 55.9, 56.0 (2C), 70.0 (q, C-6, $^2J_{C,F}$=34.1 Hz), 107.4, 111.0, 111.7 (br s), 114.0 (br s), 115.1, 115.2, 116.1, 116.3, 120.3, 121.6, 122.3, 122.8, 123.3 (q, CF_3, $^1J_{C,F}$=287.5 Hz), 123.33 (br s), 123.9, 126.4, 128.9, 129.0, 147.3, 147.6, 148.5, 149.4, 150.0; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.00 (t, 2H, H-9, J=5.5 Hz), 3.21, 3.73, 3.82 (all s, 3H, MeO), 3.6–3.9 (m, 4H, MeO, H-8′), 4.37 (dt, 1H, H-8″, J=12.5, 5.5 Hz), 6.43 (s, 1H, H-13), 6.56 (q, 1H, H-6, $^3J_{H,F}$=6.9 Hz), 6.6–6.8 (br s, 1H, Ar), 6.74 (ddd, 1H, H-2, J=8.2, 7.5, 2.0 Hz), 6.87 (d,

1H, H-1, J=7.5 Hz), 6.89 (s, 1H, H-10), 6.9–7.0 (m, 2H, H-3, H-4), 7.0–7.3 (br s, 2H, Ar); ^{19}F NMR (376 MHz, DMSO-d_6) δ 85.4 (br d, CF_3, $^3J_{F,H}$=6.9 Hz); ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 3.00 (m, 2H, H-9), 3.28 (s, 3H, MeO–C12), 3.74 (s, 6H, MeO–C3′, MeO–C11), 3.82 (m, 1H, H-8′), 3.84 (s, 3H, MeO–C4′), 4.30 (dt, 1H, H-8″, J=12.3, 5.8 Hz), 6.41 (q, 1H, H-6, $^3J_{H,F}$=6.7 Hz), 6.51 (s, 1H, H-13), 6.72 (ddd, 1H, H-2, J=7.5, 7.2, 1.4 Hz), 6.86 (s, 1H, H-10), 6.88 (dd, 1H, H-1, J=7.7, 1.4 Hz), 6.94 (dd, 1H, H-4, J=8.0, 1.3 Hz), 6.95 (br d, 1H, H-6′, J=9.0 Hz), 6.98 (ddd, 1H, H-3, J=8.1, 7.1, 1.2 Hz), 7.01 (br s, 1H, H-2′), 7.11 (d, 1H, H-5′, J=8.2 Hz); ^{13}C NMR (126 MHz, DMSO-d_6, 100 °C) δ 26.6 (C-9), 39.9 (C-8), 53.5 (MeO), 54.5 (MeO), 54.7 (2MeO), 67.4 (q, C-6, $^2J_{C,F}$=33.2 Hz), 106.9 (C-13), 111.5 (C-10), 112.2 (C-5′), 112.6 (C-14a), 113.9 (C-6a), 114.1 (C-4), 114.2 (C-2′), 114.3 (C14), 118.8 (C-14b), 119.7 (C-13a), 120.4 (C-2/1), 120.5 (C-1/2), 121.9 (C-6′), 122.0 (q, CF_3, $^1J_{C,F}$=285.5), 123.5 (C-9a), 124.6 (C-3), 127.1 (C-13b/1′), 127.3 (C-1′/13b), 146.2 (C-12/11), 147.5 (C-4′), 148.2 (C-4a/3′), 148.4 (C-3′/4a). Anal. Calcd for $C_{30}H_{26}F_3NO_5$: C, 67.03; H, 4.88; N, 2.61. Found: C, 66.75; H, 4.87; N, 2.89.

*3.6.2. 14-(3′,4′-Dimethoxyphenyl)-2,11,12-trimethoxy-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**10b**).* Yield 0.38 g (66%), mp 174–175 °C; IR (KBr) 1613, 1581, 1558, 1544, 1516 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02–3.08 (m, 2H, H-9), 3.36 (s, 3H, MeO–C12), 3.47 (s, 3H, MeO–C2), 3.86 (s, 6H, 2 MeO), 3.92–4.01 (m, 1H, H-8′), 4.01 (s, 3H, MeO), 4.07 (dt, 1H, H-8″, J=12.2, 5.8 Hz), 5.70 (q, 1H, H-6, $^3J_{H,F}$=6.2 Hz), 6.52 (d, 1H, H-1, J=3.0 Hz), 6.54 (dd, 1H, H-3, J=8.7, 3.0 Hz), 6.59 (br s, 1H, H-13), 6.69 (s, 1H, H-10), 6.8–7.2 (m, 3H, Ar), 6.90 (d, 1H, H-4, J=8.7 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 83.5 (br d, CF_3, $^3J_{F,H}$=5.8 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.97–3.03 (m, 2H, H-9), 3.22 (s, 3H, MeO–C12), 3.44 (s, 3H, MeO–C2), 3.71–3.85 (m, 1H, H-8′), 3.73 (s, 6H, 2 MeO), 3.81 (s, 3H, MeO), 4.37 (dt, 1H, H-8″, J=12.6, 5.3 Hz), 6.42 (d, 1H, H-1, J=3.0 Hz), 6.48 (s, 1H, H-13), 6.48 (q, 1H, H-6, $^3J_{H,F}$=6.8 Hz), 6.55 (dd, 1H, H-3, J=8.8, 3.0 Hz), 6.66–6.85 (br s, 1H, Ar), 6.88 (d, 1H, H-4, J=8.8 Hz), 6.89 (s, 1H, H-10), 7.0–7.3 (m, 2H, Ar); ^{19}F NMR (376 MHz, DMSO-d_6) δ 85.6 (d, CF_3, $^3J_{F,H}$=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.0, 42.0, 55.1, 55.2, 55.9, 56.1, 69.9 (q, C-6, $^2J_{C,F}$=33.9 Hz), 107.4, 107.7, 111.0, 111.8, 114.0 (br s), 115.3, 115.7, 116.3, 116.5, 120.9, 121.6, 123.5 (br s), 123.3 (q, CF_3, $^1J_{C,F}$=287.6 Hz), 123.9, 128.8, 128.9, 143.9, 147.4, 147.6, 148.5, 149.5, 154.6. Anal. Calcd for $C_{31}H_{28}F_3NO_6$: C, 65.60; H, 4.97; N, 2.47. Found: C, 65.45; H, 4.62; N, 2.52.

*3.6.3. 2-Bromo-14-(3′,4′-dimethoxyphenyl)-11,12-dimethoxy-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**10c**).* Yield 0.57 g (92%), mp 204–205 °C; IR (KBr) 1602, 1576, 1545, 1516, 1502, 1486 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.02–3.08 (m, 2H, H-9), 3.36, 3.86, 3.88, 3.96 (all s, 3H, MeO), 3.93–4.00 (m, 1H, H-8′), 4.07 (dt, 1H, H-8″, J=12.0, 6.0 Hz), 5.74 (q, 1H, H-6, $^3J_{H,F}$=6.1 Hz), 6.55 (s, 1H, H-13), 6.69 (s, 1H, H-10), 6.8–7.2 (m, 3H, Ar), 6.85 (d, 1H, H-4, J=8.3 Hz), 7.07 (d, 1H, H-1, J=2.4 Hz), 7.09 (dd, 1H, H-3, J=8.3, 2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 83.4 (d, CF_3, $^3J_{F,H}$=6.1 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.97–3.03 (m, 2H, H-9), 3.22, 3.74, 3.78, 3.83 (all s, 3H, MeO), 3.66 (m, 1H, H-8′), 4.38 (m, 1H, H-8″), 6.45 (s, 1H, H-13), 6.64 (q, 1H, H-6, $^3J_{H,F}$=6.7 Hz), 6.7–6.9 (br s, 1H, Ar), 6.90 (s, 1H, H-10), 6.96 (d, 1H, H-4, J=8.6 Hz), 6.98 (d, 1H, H-1, J=2.0 Hz), 7.0–7.3 (m, 2H, Ar), 7.15 (dd, 1H, H-3, J=8.6, 2.4 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ 85.3 (d, CF_3, $^3J_{F,H}$=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.9, 42.1, 55.2, 55.9, 56.2 (2C), 70.1 (q, C-6, $^2J_{C,F}$=34.3 Hz), 107.5, 111.0, 111.9 (br s), 114.0 (br s), 114.1, 114.8, 115.4, 116.3, 117.7, 121.3, 122.4, 123.1 (q, CF_3, $^1J_{C,F}$=287.3 Hz), 123.4 (br s), 124.0, 125.4, 128.1, 128.9, 129.3, 147.5, 147.6, 148.8, 149.0, 149.6. Anal. Calcd for $C_{30}H_{25}BrF_3NO_5$: C, 58.45; H, 4.09; N, 2.27. Found: C, 58.50; H, 3.99; N, 2.45.

*3.6.4. 14-(3′,4′-Diethoxyphenyl)-11,12-diethoxy-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**10d**).* Yield 0.48 g (81%), mp 154–155 °C; IR (KBr) 1608, 1581, 1553, 1542, 1504, 1515, 1475 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17, 1.42, 1.52 (all t, 3H, Me, J=7.0 Hz), 1.3–1.5 (br s, 3H, Me), 2.98–3.07 (m, 2H, H-9), 3.58 (ABX_3-system, 2H, CH_2O–C12, J=10.0, 7.0 Hz), 3.92–4.01 (m, 2H, H-8), 4.06 (q, 2H, OCH_2, J=7.0 Hz), 4.0–4.2 (m, 4H, 2 CH_2O), 5.74 (q, 1H, H-6, $^3J_{H,F}$=6.2 Hz), 6.60 (s, 1H, H-13), 6.69 (s, 1H, H-10), 6.70 (ddd, 1H, H-2, J=8.2, 7.5, 2.0 Hz), 6.90 (d, 1H, H-1, J=7.6 Hz), 6.96–7.01 (m, 2H, H-3, H-4), 6.7–7.2 (m, 3H, Ar); ^{19}F NMR (376 MHz, $CDCl_3$) δ 83.3 (br s, CF_3); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.05, 1.29, 1.38 (all t, 3H, Me, J=7.0 Hz), 1.15–1.35 (br s, 3H, Me), 2.94–3.01 (m, 2H, H-9), 3.40–3.54 (m, 2H, CH_2O–C12), 3.76 (m, 1H, H-8′), 3.98 (q, 2H, OCH_2, J=7.0 Hz), 3.8–4.2 (m, 4H, 2 OCH_2), 4.36 (dt, 1H, H-8″, J=12.5, 5.0 Hz), 6.45 (br s, 1H, H-13), 6.55 (q, 1H, H-6, $^3J_{H,F}$=6.8 Hz), 6.6–6.8 (br s, 1H, Ar), 6.73 (ddd, 1H, H-2, J=8.2, 7.2, 1.7 Hz), 6.85 (d, 1H, H-1, J=7.5 Hz), 6.86 (s, 1H, H-10), 6.96 (dd, 1H, H-4, J=8.2, 1.2 Hz), 6.99 (td, 1H, H-3, J=8.0, 1.3 Hz), 7.0–7.2 (br s, 2H, Ar); ^{19}F NMR (376 MHz, DMSO-d_6) δ 85.3 (d, CF_3, $^3J_{F,H}$=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 14.7, 14.8, 14.9, 28.9, 42.0, 63.6, 64.2 (br s), 64.4 (br s), 64.6, 70.0 (q, C-6, $^2J_{C,F}$=34.0 Hz), 109.0, 113.1 (2C), 113.9 (br s), 115.0, 115.2, 115.6 (br s), 116.0, 116.4, 120.4, 121.7, 122.3, 122.8, 123.3 (q, CF_3, $^1J_{C,F}$=287.0 Hz), 123.7, 126.3, 129.0 (2C), 146.9, 147.2, 148.0, 149.2, 149.9. Anal. Calcd for $C_{34}H_{34}F_3NO_5$: C, 68.79; H, 5.77; N, 2.36. Found: C, 68.58; H, 6.01; N, 2.30.

*3.6.5. 14-(3′,4′-Diethoxyphenyl)-11,12-diethoxy-2-methoxy-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**10e**).* Yield 0.44 g (71%), mp 146–147 °C; IR (KBr) 1613, 1578, 1562, 1544, 1515 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17, 1.43, 1.49 (all t, 3H, Me, J=7.0 Hz), 1.3–1.5 (br s, 3H, Me), 3.00–3.05 (m, 2H, H-9), 3.45 (s, 3H, MeO–C2), 3.58 (ABX_3-system, 2H, CH_2O–C12, J=10.0, 7.0 Hz), 3.92–4.02 (m, 2H, H-8), 4.06 (q, 2H, OCH_2, J=7.0 Hz), 4.02–4.22 (m, 4H, 2 CH_2O), 5.69 (q, 1H, H-6, $^3J_{H,F}$=6.4 Hz), 6.50 (d, 1H, H-1, J=3.0 Hz), 6.52 (dd, 1H, H-3, J=8.6, 3.0 Hz), 6.61 (s, 1H, H-13), 6.69 (s, 1H, H-10), 6.8–7.2 (m, 3H, Ar), 6.88 (d, 1H, H-4, J=8.6 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 83.5 (br d, CF_3, $^3J_{F,H}$=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 14.7, 14.8 (2C), 28.9, 42.0, 55.1, 63.6, 64.5 (br s), 64.6, 64.8, 69.9 (q, C-6, $^2J_{C,F}$=33.8 Hz), 107.6, 108.9, 111.8, 113.1, 114.2 (br s), 115.3, 115.5, 115.9 (br s), 116.3, 116.4, 120.9, 121.7, 123.2 (br s), 123.3 (q, CF_3, $^1J_{C,F}$=287.7 Hz), 123.7, 128.9, 129.0 (br s), 143.8, 146.9, 147.1, 148.0, 149.4, 154.5. Anal. Calcd for $C_{35}H_{36}F_3NO_6$: C, 67.41; H, 5.82; N, 2.25. Found: C, 67.14; H, 5.66; N, 2.22.

*3.6.6. 2-Bromo-14-(3′,4′-diethoxyphenyl)-11,12-diethoxy-6-(trifluoromethyl)-8,9-dihydro-6H-chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**10f**).* Yield 0.43 g (64%), mp 166–167 °C; IR (KBr) 1606, 1577, 1541, 1513, 1501, 1475 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, 3H, Me, J=7.0 Hz), 1.43 (t, 6H, 2 Me, J=7.0 Hz), 1.50 (t, 3H, Me, J=7.0 Hz), 3.00–3.05 (m, 2H, H-9), 3.57 (ABX_3-system, 2H, CH_2O–C12, J=10.0, 7.0 Hz), 3.92–3.98 (m, 2H, H-8), 4.06 (q, 2H, OCH_2, J=7.0 Hz), 4.02–4.22 (m, 4H, 2 CH_2O), 5.73 (q, 1H, H-6, $^3J_{H,F}$=6.0 Hz), 6.58 (s, 1H, H-13), 6.68 (s, 1H, H-10), 6.75–6.92 (m, 1H, Ar), 6.84 (d, 1H, H-4, J=8.5 Hz), 6.94–7.17 (m, 2H, Ar), 7.03 (d, 1H, H-1, J=2.4 Hz), 7.07 (dd, 1H, H-3, J=8.5, 2.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 83.4 (d, CF_3, $^3J_{F,H}$=6.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 14.8, 14.9 (2C), 28.9 (C-9), 42.1 (C-8), 63.7, 64.6, 64.7 (br s), 64.9, 70.1 (q, C-6, $^2J_{C,F}$=34.3 Hz), 109.1, 113.1, 114.2, 114.5 (br s), 114.8, 115.3, 116.1 (br s), 116.4, 117.6, 121.4, 122.4, 123.1 (q, CF_3, $^1J_{C,F}$=287.5 Hz), 123.4 (br s), 123.8, 125.4, 128.3, 128.8, 129.3, 147.1, 147.2, 148.4, 149.0, 149.5. Anal. Calcd for $C_{34}H_{33}BrF_3NO_5$: C, 60.75; H, 4.95; N, 2.08. Found: C, 60.75; H, 5.05; N, 2.16.

3.7. Compounds 11a,b and 12

*3.7.1. 2-Nitro-3-(trifluoromethyl)-3H-benzo[f]chromene (**11a**).* Yield 0.17 g (58%), mp 182–183 °C, orange powder; IR (KBr) 1643, 1569, 1506, 1365, 1354 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.24 (q, 1H, H-3,

$^3J_{H,F}$=6.4 Hz), 7.26 (dd, 1H, H-5, J=8.9, 0.8 Hz), 7.52 (ddd, 1H, H-8/9, J=8.1, 7.0, 1.1 Hz), 7.68 (ddd, 1H, H-9/8, J=8.4, 7.0, 1.3 Hz), 7.85 (d, 1H, H-7, J=8.1 Hz), 7.98 (d, 1H, H-6, J=8.9 Hz), 8.06 (dd, 1H, H-10, J=8.4, 0.8 Hz), 8.85 (s, 1H, H-1); ^{19}F NMR (376 MHz, $CDCl_3$) δ 84.4 (d, CF_3, $^3J_{F,H}$=6.4 Hz). Calcd for $C_{14}H_8F_3NO_3$: C, 56.96; H, 2.73; N, 4.74. Found: C, 56.96; H, 2.49; N, 4.75.

*3.7.2. 3-Nitro-2-(trifluoromethyl)-2H-benzo[h]chromene (**11b**).* Yield 0.12 g (40%), mp 134–135 °C, orange powder; IR (KBr) 1653, 1618, 1598, 1561, 1516, 1504, 1466, 1388 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (q, 1H, H-2, $^3J_{H,F}$=6.4 Hz), 7.35 (d, 1H, H-6, J=8.4 Hz), 7.55 (d, 1H, H-5, J=8.4 Hz), 7.59 (ddd, 1H, H-8/9, J=8.2, 6.9, 1.4 Hz), 7.64 (ddd, 1H, H-9/8, J=8.1, 6.9, 1.4 Hz), 7.82 (d, 1H, H-7, J=8.1 Hz), 8.25 (s, 1H, H-4), 8.26 (d, 1H, H-10, J=8.1 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 83.3 (d, CF_3, $^3J_{F,H}$=6.4 Hz). Calcd for $C_{14}H_8F_3NO_3$: C, 56.96; H, 2.73; N, 4.74. Found: C, 57.06; H, 2.88; N, 4.80.

*3.7.3. 14-(3,4-Dimethoxyphenyl)-11,12-dimethoxy-6-(trifluoromethyl)-8,9-dihydro-6H-benzo[7′,8′]chromeno[4′,3′:4,5]pyrrolo[2,1-a]isoquinoline (**12**).* This compound was prepared from chromene **11b** and dihydropapaverine **9** (R=Me) according to the procedure described for compounds **10**. Yield 0.55 g (94%), mp 235–236 °C, colourless powder; IR (KBr) 1605, 1576, 1541, 1519, 1498 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (t, 2H, H-9, J=6.5 Hz), 3.37, 3.87, 3.97 (all s, 3H, MeO), 3.7–4.0 (br s, 3H, MeO), 4.03 (dt, 1H, H-8′, J=12.1, 6.7 Hz), 4.12 (dt, 1H, H-8″, J=12.1, 6.1 Hz), 6.00 (q, 1H, H-6, $^3J_{H,F}$=6.3 Hz), 6.60 (s, 1H, H-13/10), 6.70 (s, 1H, H-10/13), 6.8–7.2 (m, 3H, Ar), 7.09 (d, 1H, H-16, J=8.6 Hz), 7.23 (d, 1H, H-15, J=8.6 Hz), 7.37 (ddd, 1H, H-2/3, J=8.1, 6.8, 1.3 Hz), 7.45 (ddd, 1H, H-3/2, J=8.4, 6.8, 1.4 Hz), 7.68 (d, 1H, H-1, J=8.1 Hz), 8.22 (d, 1H, H-4, J=8.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 82.6 (br d, CF_3, $^3J_{F,H}$=5.3 Hz); ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.03 (dd, 2H, H-9, J=7.9, 5.4 Hz), 3.23, 3.74, 3.84 (all s, 3H, MeO), 3.6–3.9 (br s, 3H, MeO), 3.82 (m, 1H, H-8′), 4.42 (dt, 1H, H-8″, J=12.5, 5.4 Hz), 6.48 (s, 1H, H-13), 6.84 (q, 1H, H-6, $^3J_{H,F}$=6.9 Hz), 6.6–6.9 (br s, 1H, ArC-14), 6.90 (s, 1H, H-10), 7.0–7.4 (m, 2H, ArC-14), 7.06 (d, 1H, H-16, J=8.6 Hz), 7.33 (d, 1H, H-15, J=8.6 Hz), 7.42 (ddd, 1H, H-2/3, J=8.0, 7.0, 1.0 Hz), 7.51 (ddd, 1H, H-3/2, J=8.4, 7.0, 1.1 Hz), 7.75 (d, 1H, H-1, J=8.0 Hz), 8.09 (d, 1H, H-4, J=8.4 Hz); ^{19}F NMR (376 MHz, DMSO-d_6) δ 86.5 (d, CF_3, $^3J_{F,H}$=6.9 Hz). Calcd for $C_{34}H_{28}F_3NO_5$: C, 69.50; H, 4.80; N, 2.38. Found: C, 69.32; H, 4.68; N, 2.50.

3.8. Crystal data for *tc*-6b and *ct*-6g

*3.8.1. Crystal data for tc-**6b**.* $C_{24}H_{25}Cl_3N_2O_3$, M 495.84, triclinic crystals space group P–1, a=10.3139(7), b=11.1354(8), c=21.033(2) Å, α=82.224(7), β=89.459(7), γ=89.264(5)°, V=2393.1(3) Å^3, d_{calcd}=1.376 g cm^{-3}, absorption coefficient μ=0.412 mm^{-1}, Z=4. The intensities of 11506 independent reflections (R_{int}=0.0272) were measured on an 'Xcalibur 3' automatic four-circle diffractometer (Mo Kα radiation, λ=0.71073 Å, graphite monochromator, $\omega/2\theta$ scan, $2\theta_{max}$=56.6°). The structure was solved by direct methods and refined by full-matrix least-squares method using the SHELX-97 program package.[24] All non-hydrogen atoms were refined with anisotropic atomic displacement and hydrogen atoms were included at calculated position using a riding model. The final discrepancy factors R_1=0.0459, wR_2=0.0969, GoF=1.007 for 3947 reflections with $I>2\sigma(I)$; R_1=0.1421, wR_2=0.1036 (all data). Largest different peak and hole: 0.369 and −0.349 e Å^{-3}. Completeness to θ=28.28° (96.9%). Deposition number CCDC 816061.

*3.8.2. Crystal data for ct-**6g**.* $C_{27}H_{26}N_2O_3$, M 426.52, triclinic crystals space group P–1, a=9.8255(13), b=9.8304(7), c=12.2545(13) Å, α=93.861(7), β=104.297(10), γ=101.445(9)°, V=1115.7(2) Å^3, d_{calcd}=1.270 g cm^{-3}, absorption coefficient μ=0.083 mm^{-1}, Z=2. The intensities of 5416 independent reflections (R_{int}=0.0250) were measured on an 'Xcalibur 3' automatic four-circle diffractometer (Mo Kα radiation, λ=0.71073 Å, graphite monochromator, $\omega/2\theta$ scan, $2\theta_{max}$=56.6°). The structure was solved by direct methods and refined by full-matrix least-squares method using the SHELX-97 program package.[24] All non-hydrogen atoms were refined with anisotropic atomic displacement and hydrogen atoms were included at calculated position using a riding model. The final discrepancy factors R_1=0.0408, wR_2=0.0807, GoF=1.004 for 2089 reflections with $I>2\sigma(I)$; R_1=0.1185, wR_2=0.0856 (all data). Largest different peak and hole: 0.280 and −0.214 e Å^{-3}. Completeness to θ=28.28° (98.0%). Deposition number CCDC 816060.

Acknowledgements

This work was financially supported by the Russian Foundation for Basic Research (Grant 11-03-00126) and the Presidium program of the RAS N 21.

References and notes

1. (a) *Organofluorine Compounds in Medicinal Chemistry and Biomedical Applications*; Filler, R., Kobayashi, Y., Yagupolskii, L. M., Eds.; Elsevier: Amsterdam, 1993; (b) Hiyama, T. *Organofluorine Compounds: Chemistry and Application*; Springer: Berlin, 2000.
2. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
3. (a) Engler, T. A.; Reddy, J. P.; Combrink, K. D.; Velde, D. V. *J. Org. Chem.* **1990**, *55*, 1248–1254; (b) Murugesh, M. G.; Subburaj, K.; Trivedi, G. K. *Tetrahedron* **1996**, *52*, 2217–2228; (c) Engler, T. A.; LaTessa, K. O.; Iyengar, R.; Chai, W.; Agrios, K. *Bioorg. Med. Chem.* **1996**, *4*, 1755–1769.
4. Korotaev, V. Y.; Kutyashev, I. B.; Sosnovskikh, V. Y. *Heteroat. Chem.* **2005**, *16*, 492–496.
5. (a) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Kodess, M. I. *Lett. Org. Chem.* **2005**, *2*, 616–620; (b) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Kodess, M. I. *Izv. Akad. Nauk, Ser. Khim.* **2006**, 309–321; *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 317–330; (c) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B. *Izv. Akad. Nauk, Ser. Khim.* **2007**, 1985–1990; *Russ. Chem. Bull., Int. Ed.* **2007**, *56*, 2054–2059; (d) Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Kodess, M. I. *Izv. Akad. Nauk, Ser. Khim.* **2006**, 1945–1955; *Russ. Chem. Bull., Int. Ed.* **2006**, *55*, 2020–2031; (e) Korotaev, V. Y.; Kutyashev, I. B.; Sosnovskikh, V. Y.; Kodess, M. I. *Mendeleev Commun.* **2007**, *17*, 52–53.
6. (a) Shamma, M. *The Isoquinoline Alkaloids*; Academic: New York, NY, 1972; (b) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: 1998.
7. (a) Shklyaev, Y. V.; Maslivets, A. N. *Zh. Org. Khim.* **1996**, *32*, 319; *Russ. J. Org. Chem.* **1996**, *32*, 302; (b) Sviridov, V. D.; Chkanikov, N. D.; Galakhov, M. V.; Shklyaev, Y. V.; Shklyaev, V. S.; Aleksandrov, B. B.; Gavrilov, M. S. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1990**, 1405–1410; *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1990**, *39*, 1268–1273; (c) Tyutin, V. Y.; Chkanikov, N. D.; Shklyaev, Y. V.; Shklyaev, V. S.; Kolomiets, A. F.; Fokin, A. V. *Izv. Acad. Nauk, Ser. Khim.* **1992**, 1888–1891; *Bull. Russ. Acad. Sci. Div. Chem. Sci.* **1992**, *41*, 1474–1477; (d) Sviridov, V. D.; Chkanikov, N. D.; Shklyaev, Y. V.; Kolomiets, A. F.; Fokin, A. V. *Khim. Geterotsikl. Soedin.* **1990**, 1689; *Chem. Heterocycl. Compd.* **1990**, *26*, 1405.
8. Meyer, H. *Liebigs Ann. Chem.* **1981**, 1534–1544.
9. (a) Grob, C. A.; Camenisch, K. *Helv. Chim. Acta* **1953**, *36*, 49–58; (b) Grob, C. A.; Schad, H. P. *Helv. Chim. Acta* **1955**, *38*, 1121–1127.
10. (a) Gómez-Sánchez, A.; Mancera, M.; Rosado, F. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1199–1205; (b) Revial, G.; Lim, S.; Viossat, B.; Lemoine, P.; Tomas, A.; Duprat, A. F.; Pfau, M. *J. Org. Chem.* **2000**, *65*, 4593–4600; (c) Baldoli, C.; Cremonesi, G.; Croce, P. D.; La Rosa, C.; Licandro, E. *Heterocycles* **2004**, *64*, 491–497; (d) Alizadeh, A.; Rezvanian, A.; Bijanzadeh, H. R. *Synthesis* **2008**, 725–728; (e) Gupta, R. C.; Seth, M.; Bhaduri, A. P. *Indian J. Chem.* **1991**, *30B*, 247–298.
11. Lim, S.; Jabin, I.; Revial, G. *Tetrahedron Lett.* **1999**, *40*, 4177–4180.
12. (a) Andersen, R. J.; Faulkner, D. J.; Cun-heng, H.; Van Duyne, G. D.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 5492–5495; (b) Ham, J.; Kang, H. *Bull. Korean Chem. Soc.* **2002**, *23*, 163–166; (c) Ploypradith, P.; Petchmanee, T.; Sahakitpichan, P.; Litvinas, N. D.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 9440–9448; (d) Krishnaiah, P.; Reddy, V. L. N.; Venkataramana, G.; Ravinder, K.; Srinivasulu, M.; Raju, T. V.; Ravikumar, K.; Chandrasekar, D.; Ramakrishna, S.; Venkateswarlu, Y. *J. Nat. Prod.* **2004**, *67*, 1168–1171.
13. (a) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. *Chem. Rev.* **2008**, *108*, 264–287; (b) Banwell, M.; Flynn, B.; Hockless, D. *Chem. Commun.* **1997**, 2259–2260; (c) Reddy, M. V. R.; Rao, M. R.; Rhodes, D.; Hansen, M. S. T.; Rubins, K.; Bushman, F. D.; Venkateswarlu, Y.; Faulkner, D. J. *J. Med. Chem.* **1999**, *42*, 1901–1907; (d) Reddy, S. M.; Srinivasulu, M.; Satyanarayana, N.; Kondapi, A. K.; Venkateswarlu, Y. *Tetrahedron* **2005**, *61*, 9242–9247.
14. Tardy, C.; Facompré, M.; Laine, W.; Baldeyrou, B.; García-Gravalos, D.; Francesch, A.; Mateo, C.; Pastor, A.; Jiménez, J. A.; Manzanares, I.; Cuevas, C.; Bailly, C. *Bioorg. Med. Chem.* **2004**, *12*, 1697–1712.
15. (a) Banwell, M. G.; Flynn, B. L.; Hamel, E.; Hockless, D. C. R. *Chem. Commun.* **1997**, 207–208; (b) Handy, S. T.; Zhang, Y.; Bregman, H. *J. Org. Chem.* **2004**, *69*, 2362–2366; (c) Nyerges, M.; Tőke, L. *Tetrahedron Lett.* **2005**, *46*, 7531–7534; (d)

Cironi, P.; Manzanares, I.; Albericio, F.; Álvarez, M. *Org. Lett.* **2003**, *5*, 2959–2962; (e) Marfil, M.; Albericio, F.; Álvarez, M. *Tetrahedron* **2004**, *60*, 8659–8668; (f) Ploypradith, P.; Jinaglueng, W.; Pavaro, C.; Ruchirawat, S. *Tetrahedron Lett.* **2003**, *44*, 1363–1366; (g) Fujikawa, N.; Ohta, T.; Yamaguchi, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *Tetrahedron* **2006**, *62*, 594–604; (h) Ohta, T.; Fukuda, T.; Ishibashi, F.; Iwao, M. *J. Org. Chem.* **2009**, *74*, 8143–8153; (i) Li, Q.; Jiang, J.; Fan, A.; Cui, Y.; Jia, Y. *Org. Lett.* **2011**, *13*, 312–315.
16. Ploypradith, P.; Mahidol, C.; Sahakitpichan, P.; Wongbundit, S.; Ruchirawat, S. *Angew. Chem., Int. Ed.* **2004**, *43*, 866–868.
17. Korotaev, V. Y.; Sosnovskikh, V. Y.; Kutyashev, I. B.; Barkov, A. Y.; Shklyaev, Y. V. *Tetrahedron Lett.* **2008**, *49*, 5376–5379.
18. Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.-T.; Ching-Fa, Y. *Tetrahedron* **2005**, *61*, 11751–11757.
19. (a) Sakakibara, T.; Koezuka, M.; Sudoh, R. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3095–3096; (b) Yan, M.-C.; Jang, Y.-J.; Kuo, W.-Y.; Tu, Z.; Shen, K.-H.; Cuo, T.-S.; Ueng, C.-H.; Ching-Fa, Y. *Heterocycles* **2002**, *57*, 1033–1048.
20. Korotaev, V. Y.; Sosnovskikh, V. Y.; Yasnova, E. S.; Barkov, A. Y.; Shklyaev, Y. V. *Mendeleev Commun.* **2010**, *20*, 321–322.
21. Sladkov, V. I.; Sazonova, N. M.; Kuleshova, L. N.; Lindeman, S. V.; Struchkov, Y. T.; Suvorov, N. N. *Zh. Org. Khim.* **1989**, *25*, 854–862; *J. Org. Chem. USSR* **1989**, *25*, 767–773.
22. (a) Günther, H. *NMR Spectroscopy: Basic Principles, Concepts, and Applications in Chemistry*; John: New York, NY, 1996; (b) Ōki, M. *Methods in Stereochemical Analysis: Application of Dynamic NMR Spectroscopy to Organic Chemistry*; VCH: Weinheim, 1985.
23. Kessler, H. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 219–235.
24. Sheldrick, G. M. *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.